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ANESTHESIOLOGY

Antithrombin Levels and Heparin Responsiveness during Venoarterial Extracorporeal Membrane Oxygenation: A Prospective Single-center Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Unfractionated heparin, the mainstay anticoagulant for extracorporeal membrane oxygenation, is often associated with heparin resistance, a term defined as alterations in heparin responsiveness
- Although there are multiple causes, a common perception is that it is associated with acquired antithrombin deficiency

What This Article Tells Us That Is New

- In 50 adults receiving venoarterial extracorporeal membrane oxygenation, median antithrombin levels were 48% (37 to 60%) initially, and time-weighted antithrombin levels were 63% (57 to 73%) and less than or equal to 70% in 32 (64%) of patients
- Despite a moderate acquired antithrombin deficiency, mainly during the first 72 h, there was no correlation with heparin responsiveness based on anti-Xa levels and dosing requirements.

ABSTRACT

Background: Unfractionated heparin, administered during venoarterial extracorporeal membrane oxygenation to prevent thromboembolic events, largely depends on plasma antithrombin for its antithrombotic effects. Decreased heparin responsiveness seems frequent on extracorporeal membrane oxygenation; however, its association with acquired antithrombin deficiency is poorly understood. The objective of this study was to describe longitudinal changes in plasma antithrombin levels during extracorporeal membrane oxygenation support and evaluate the association between antithrombin levels and heparin responsiveness. The hypothesis was that extracorporeal membrane oxygenation support would be associated with acquired antithrombin deficiency and related decreased heparin responsiveness.

Methods: Adults receiving venoarterial extracorporeal membrane oxygenation were prospectively included. All patients received continuous intravenous unfractionated heparin using a standardized protocol (target anti-Xa 0.3 to 0.5 IU/ml). For each patient, arterial blood was withdrawn into citrate-containing tubes at 11 time points (from hour 0 up to day 7). Anti-Xa (without dextran or antithrombin added) and antithrombin levels were measured. The primary outcome was the antithrombin plasma level. In the absence of consensus, antithrombin deficiency was defined as a time-weighted average of antithrombin less than or equal to 70%. Data regarding clinical management and heparin dosage were collected.

Results: Fifty patients, including 42% postcardiotomy, were included between April 2020 and May 2021, with a total of 447 samples. Median extracorporeal membrane oxygenation duration was 7 (interquartile range, 4 to 12) days. Median antithrombin level was 48% (37 to 60%) at baseline. Antithrombin levels significantly increased throughout the follow-up. Time-weighted average of antithrombin levels was 63% (57 to 73%) and was less than or equal to 70% in 32 (64%) of patients. Overall, 45 (90%) patients had at least one antithrombin value less than 70%, and 35 (70%) had at least one antithrombin value less than 50%. Antithrombin levels were not significantly associated with heparin responsiveness evaluated by anti-Xa assay or heparin dosage.

Conclusions: Venoarterial extracorporeal membrane oxygenation support was associated with a moderate acquired antithrombin deficiency, mainly during the first 72 h, that did not correlate with heparin responsiveness.

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Venoarterial extracorporeal membrane oxygenation (ECMO) is increasingly used for managing refractory circulatory failure.¹ Bleeding and thrombosis remain frequent and associated with high mortality.^{2,3} They occur as a result of a complex interplay between the underlying

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critical illness, blood exposure to shear stress and nonbiologic surfaces, and antithrombotic strategies.²

International guidelines recommend systemic anticoagulation with unfractionated heparin to prevent ECMO- and patient-related thromboembolic events, although the evidence for both thrombosis and bleeding is very weak.^{4,5} The Extracorporeal Life Support Organization (Ann Arbor, Michigan) recommends a therapeutic heparin level monitored using activated partial thromboplastin time (PTT) or anti-Xa level (target 0.30 to 0.70 IU/ml), whereas the International Society on Thrombosis and Haemostasis (Carrboro, North Carolina) recommends an anti-Xa range of 0.30 to 0.50 IU/ml.⁵ Current prospective data do not support the efficacy of low-anticoagulation strategies in reducing bleeding.⁴⁻⁸

Unfractionated heparin requires binding to antithrombin (AT) to inhibit coagulation factors, especially factor Xa and thrombin. As a negatively charged glycosaminoglycan, it can bind to numerous proteins, cells, and nonbiologic surfaces, reducing its anticoagulant activity, especially during acute inflammatory situations in the intensive care unit (ICU).^{9,10} The management of unfractionated heparin is challenging due to its high interindividual variability in anticoagulant response and to the risk of heparin-induced thrombocytopenia.^{2,3,9,11} The biologic heparin responsiveness, or anticoagulant effect, must be differentiated from the clinical response (thrombosis prevention). As of now, there are no routine tests that can reliably capture the full scope of the anticoagulant effect. For lack of better options, we rely on activated PTT or anti-Xa measurements. Decreased heparin responsiveness, also called heparin resistance, is an alteration in the heparin dose response, often reported as the need for high doses of heparin to achieve the desired anticoagulation levels. However, there is no evidence supporting the numerous definitions found in the literature.¹² Decreased heparin responsiveness may be particularly frequent during ECMO.^{2,13}

Acquired AT deficiency is often arbitrarily defined as plasma AT levels less than 70 to 80% or U/dl, based on the definition of constitutional deficiency and the normal AT range in plasma (80 to 120% or U/dl).¹⁴ It is frequently reported in ICU patients, especially in the setting of cirrhosis, sepsis, or cardiothoracic surgery.^{15,16} Severe inherited AT deficiency is a major risk factor for thrombosis, associated with both clinical and laboratory decreased heparin responsiveness.¹⁷ So far, evidence is lacking to support the association between acquired AT deficiency and decreased heparin responsiveness or thrombotic events. Moreover, the AT level required to achieve therapeutic anticoagulation is unclear, with limited data on severity thresholds and therapeutic targets.

Whereas acquired AT deficiency seems common during venovenous ECMO support,^{3,18,19} data remain limited for venoarterial ECMO.¹⁹⁻²¹ One small prospective randomized trial evaluated AT supplementation during venovenous ECMO, without any beneficial effect reported.^{5,18} Despite the absence of evidence regarding efficacy, safety, and cost, AT monitoring and supplementation is routinely performed during venovenous and venoarterial ECMO.^{3,22,23}

This study aimed to evaluate AT plasma levels, analyze heparin responsiveness, and evaluate the association between AT levels and heparin responsiveness during venoarterial ECMO support. We hypothesized that venoarterial ECMO support is associated with acquired AT deficiency and related alterations in heparin responsiveness.

Materials and Methods

Study Design

The ATECMO study (evaluation of AntiThrombin deficiency during ECMO support; NCT04133844) was designed as a prospective observational study. It was conducted in a 1,500-bed tertiary university hospital

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(University Hospital of Rennes, Rennes, France), comprising a cardiothoracic surgery department and three adult ICUs. The study was ethically approved (Ethics Committee CPP OUEST VI, France; approval 2019-A011440-57; October 1, 2019) with procedures followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975. Written informed consent was obtained from all participants or relatives (deferred emergency consent).

Participants

Patients older than 18 yr supported by venoarterial ECMO (first ECMO run) were screened for inclusion. The exclusion criteria were moribund patient with expected life expectancy of less than 24 h, pregnancy, ECMO for periprocedural hemodynamic support, acute arterial (except for myocardial infarction) or venous thrombosis, inherited bleeding disorder, contraindication for unfractionated heparin (history of heparin-induced thrombocytopenia or unfractionated heparin allergy), and known inherited AT deficiency.

ECMO Management

Indications for venoarterial ECMO therapy included medical and surgical causes of refractory cardiogenic shock in patients for whom satisfactory systemic perfusion could not be achieved despite optimal intravascular volume status, high-dose inotropic medication, and/or other support. In case of postcardiotomy ECMO, heparin was fully reversed using protamine using Hepcon HMS Plus (Medtronic, France). The standard protocol for venoarterial implantation in our institution has been previously published.²⁴ The ECMO program was jointly run by cardiothoracic surgeons and anesthesiologist-intensivists. Whenever possible, peripheral access through femoral vessels was used. Three different centrifugal pumps were used during the study: Rotaflow (Getinge, Sweden), Cardiohelp (Getinge), and Medos (Xenios, Germany).

Anticoagulation Management

Anticoagulation was initiated as soon as possible after ECMO cannulation, in the absence of overt bleeding or severe thrombocytopenia (platelet count less than $50 \times 10^9/L$). In the absence of high-quality clinical data to support any ECMO anticoagulation protocol, we developed a pragmatic approach at our center in 2019. This protocol, adapted from the work of Raschke *et al.*,²⁵ involves the use of therapeutic doses of unfractionated heparin with weight-based boluses and continuous intravenous infusion in situations without overt bleeding (Supplemental Digital Content 1 for unfractionated heparin dosage protocol, <https://links.lww.com/ALN/D450>). We opted for anti-Xa monitoring, which is readily available as a routine test in our laboratory, targeting a range of 0.30 to 0.50 IU/ml. This approach therefore aligns with the Extracorporeal Life Support Organization and International

Society on Thrombosis and Haemostasis recommendations that were published later.^{4,5}

AT supplementation was not routinely performed in our center. The decision to measure AT level and to administer AT supplementation (human AT) was at the discretion of the physician, in case of marked AT deficiency associated with an anti-Xa level of less than 0.30 IU/ml despite unfractionated heparin dosage of greater than $35 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Heparin-induced thrombocytopenia (HIT) was suspected and confirmed according to published guidelines.²⁶ Heparin was discontinued in case of suspected HIT with positive anti-PF4/heparin antibodies and switched to argatroban.

Study Outcomes

The primary outcome was AT plasma level, measured from ECMO initiation and up to 7 days (at 11 time points: hours 0, 2, 6, 12, and 24 and daily from days 2 to 7 or until ECMO decannulation). In the absence of consensus, AT deficiency on ECMO was arbitrarily defined as a time-weighted average of AT less than or equal to 70% (corresponding to the therapeutic target for recombinant AT in the summary of product characteristics). For each time point, AT deficiency was categorized as follows: normal values were greater than 70%, moderate deficiency was between 50% and 70%, and severe deficiency was less than 50%.

The secondary outcomes of our study included unfractionated heparin dosage and anti-Xa levels at each dosage adjustment, time spent in the therapeutic anti-Xa range, and the number of heparin interruptions. These outcomes were selected to best characterize heparin responsiveness, which is a dynamic and complex concept requiring the integration of unfractionated heparin dosage and its effect, measured by anti-Xa in this case.

Furthermore, in an exploratory manner we developed a heparin responsiveness index, defined for each anti-Xa measurement as the ratio of unfractionated heparin dosage ($\text{IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) to the anti-Xa level (IU/ml). This index facilitates a concurrent and dynamic assessment of both heparin dosage and its corresponding anti-Xa with each adjustment in dosage. It was developed by adapting the approach of the heparin sensitivity index, a concept used for heparin responsiveness during cardiopulmonary bypass.^{27,28}

Additional variables were collected including demographic characteristics, cannulation-related variables (place of cannulation, type of ECMO, cannulation site), use of AT supplementation, thrombotic and bleeding events, length of ECMO support, and 30-day mortality. No systematic screening was performed for bleeding and thrombotic complications. Bleeding events were defined as intracranial bleeding or bleeding requiring at least a decrease in hemoglobin levels greater than 2 g/dl or the need for at least two packed red blood cell transfusions in 24 h, including upper or lower gastrointestinal hemorrhage, peripheral cannulation site bleeding, retroperitoneal bleeding, and pulmonary hemorrhage. Thrombotic events included ischemic stroke,

deep vein thrombosis, pulmonary embolism acute mesenteric ischemia, acute limb ischemia, macroscopic clotting of circuit and/or membrane without need to change the circuit or the oxygenator, oxygenator failure requiring change due to clot formation, and acute circuit clotting requiring change. To minimize potential information biases, data were collected prospectively, and both hemorrhagic and thrombotic events were independently qualified by two separate investigators who were blinded to the biologic results.

Blood Sample Collection and Laboratory Analyses

Routine care unfractionated heparin anticoagulation monitoring was performed by physicians using anti-Xa levels using a reagent without added AT or dextran (STA-Liquid-anti-Xa; Stago, France). To avoid influencing clinical practices and to maintain the rigorous methodologic standards of a cohort study, additional biologic assessments required by the study, particularly AT measurements, were conducted in a blinded and centralized manner and processed in batches. Quantitative measurements of AT, based on the inhibition of thrombin (STA-Stachrom ATIII; Stago), and of anti-Xa levels (STA-Liquid-anti-Xa; Stago; without added AT or dextran) were performed on a STA-R Max coagulometer (Stago) at each prespecified time point (up to 11 time points). Blood samples were drawn at each time point from pre-existing arterial line and collected into vacuum tubes (Vacutainer; Becton Dickinson, USA) containing citrate (0.109 M) or EDTA (complete blood count). Plasma was obtained from citrated blood after centrifugation at 2,000g for 10 min, within 1 h after withdrawal. After a second centrifugation, plasma samples were stored frozen at -80°C before thawing. In case of suspected HIT, anti-PF4/heparin antibodies were assessed using Asserachrom HIPA-IgG (Stago).

Statistical Analysis

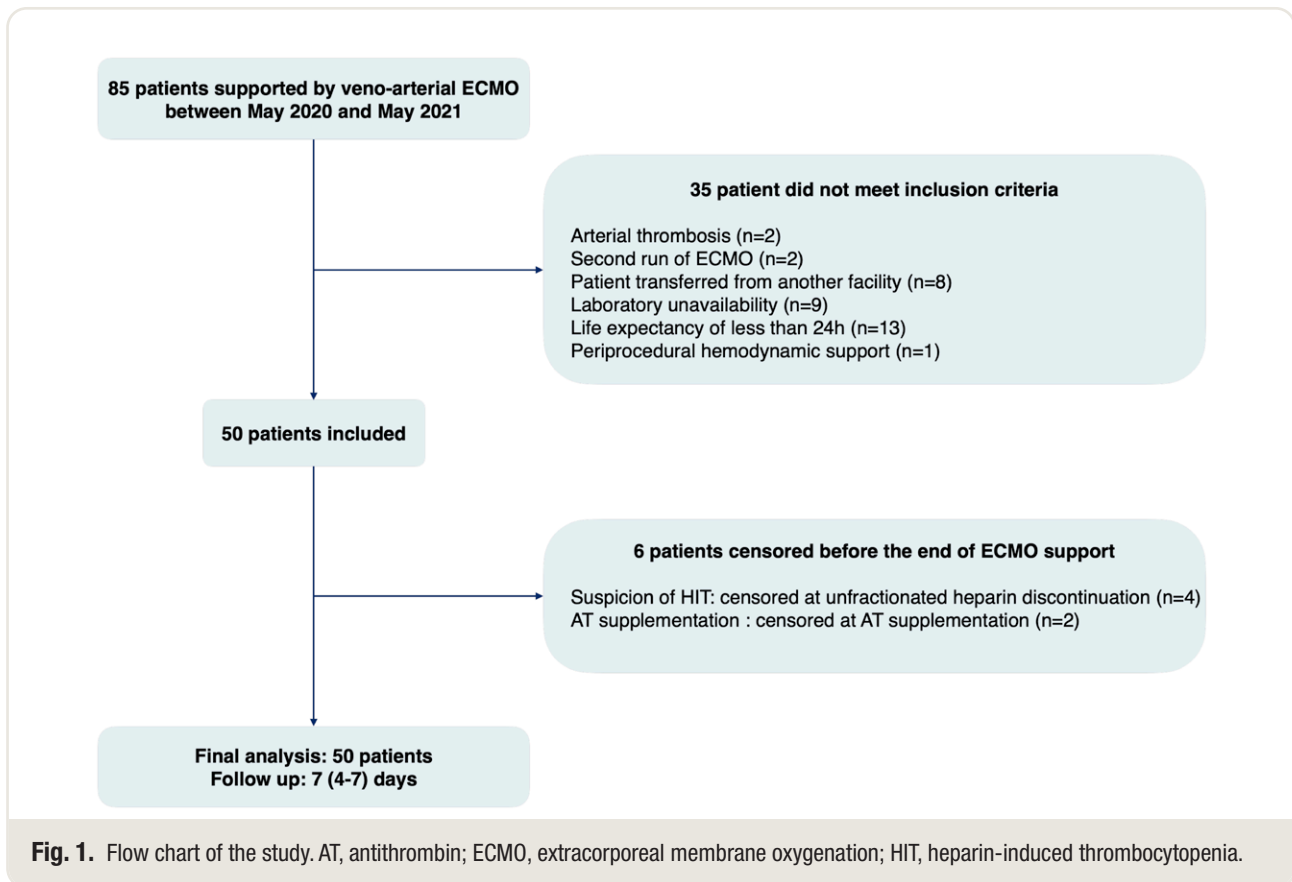
In the absence of published data regarding the temporal evolution of AT deficiency during venoarterial ECMO support and time-weighted average, calculating the sample size was not possible. An *ad hoc* sample size of 50 participants was chosen and provided us with 95% confidence and a margin of error of 5 points to estimate mean AT level, considering the SD previously reported.²⁰ Given the nature of the invasive treatments administered to these patients, and the fact that our study was conducted in a tertiary referral center, we expected no loss to follow-up. Although the methodology used for this study does not allow for multivariable analyses to assess causality and the direct effects of AT deficiency, we have attempted to minimize major confounding factors in our descriptive and correlational approach. Therefore, patients receiving AT supplementation were censored for all analyses at the time of first administration. Patients with suspected HIT were censored for laboratory analyses at the time argatroban

was initiated and were excluded from thrombosis analysis if HIT was confirmed. Patient characteristics were expressed as number (percentage) for categorical variables and median with interquartile range for continuous variables. Because the samples were not collected at a constant rate (time between sample collection ranging between 2 and 24 h), we calculated a time-weighted average of plasma AT levels using linear interpolation between each sampling points. We did not use any imputation methods for addressing missing data. When an AT measurement was missing at a specific time point, we calculated the time-weighted average using linear interpolation based on the data from the nearest available time points before and after the missing entry. Pairwise comparisons of AT levels at each sampling points with baseline were calculated using a mixed model for repeated measures with Dunnett correction for multiple comparisons. Correlations between AT levels and anti-Xa levels, unfractionated heparin dosage, and the heparin responsiveness index were assessed using Spearman's rank-order correlation. For comparison between patients with or without AT deficiency, bleeding, or thrombosis, a chi-square test or a Fisher's exact test was used for categorical variables, and a Kruskal-Wallis test was used for continuous variables. All tests used a two-tailed hypothesis. Statistical significance was achieved for $P < 0.05$. Statistical analyses were performed with R 4.2.1 (<https://cran.r-project.org/>, accessed June 1, 2022).

Results

Study Population

Between April 2020 to May 2021, of 85 patients supported by venoarterial ECMO, 50 were included in the study, with a total of 447 blood samples collected (fig. 1). The main characteristics of the included patients are reported in table 1. Most patients were men (80%), and the median age was 60 yr (interquartile range, 52 to 68 yr). Patients had severe conditions upon admission, with an average Simplified Acute Physiology Score II score of 51 (37 to 76) and an average Survival after Venoarterial ECMO score of -4 (-7 to -1). No patient was affected with nephrotic syndrome or liver failure before hospitalization. Only one patient had cirrhosis. Twenty-one patients (42%) received ECMO for postcardiotomy low cardiac output syndrome. The primary nonpostcardiotomy indications included acute coronary syndrome (22%) and cardiac arrest (28%). Two patients (4%) had their plasma AT levels measured by the clinician as part of the routine anticoagulation protocol (see Supplemental Digital Content 1, <https://links.lww.com/ALN/D450>) and subsequently received AT supplementation. These patients were censored for all analyses at the time of first administration (respectively on days 3 and 5). HIT was suspected in four (8%) of patients, who were censored for laboratory analyses at the time of argatroban initiation;



HIT was diagnosed for two (4%) patients, who were excluded from thrombosis analysis. Evolution of platelet count and fibrinogen levels during ECMO support are reported in supplementary table S1 (Supplemental Digital Content 2, <https://links.lww.com/ALN/D451>). Median duration of ECMO support was 7 (4 to 12) days, with a median ICU length of stay of 16 (10 to 23) days. Mortality while on ECMO therapy was 32%. In-hospital mortality was 48% at day 28.

Changes in AT Plasma Levels during Venoarterial ECMO Support

The changes in AT plasma levels during the first 7 days of ECMO support are depicted in figures 2 and 3 and supplemental figure S1 (<https://links.lww.com/ALN/D451>). The median AT level at baseline was 51% (39 to 65%). Median AT levels significantly increased after ECMO implantation as early as hour 6, with 55% (44 to 70%; $P = 0.044$ compared to baseline), and rose gradually to reach nearly normal median levels around day 4 of ECMO support, to 71% (56 to 86%; $P \leq 0.001$ compared to baseline). This temporal trend remained consistent after excluding the 24 patients who received fresh frozen plasma transfusions during the first 7 days of ECMO (Supplemental Digital Content 2, fig. S2, <https://links.lww.com/ALN/D451>). Overall, 45 (90%) patients had at least one AT value less than 70%, 35 (70%) less

than had at least one AT value less than 50%, 8 (16%) had at least one AT value less than less than 30%, and 2 (4%) had at least one AT value less than less than 20%. Time-weighted average of AT levels was 63% (57 to 73%) and was less than or equal to 70% in 32 (64%) of patients. Overall, patients spent 71% (41 to 100%) of ECMO time with AT levels under 70% and 11% (0 to 32%) of ECMO time with AT levels under 50% (Supplemental Digital Content 2, table S2, <https://links.lww.com/ALN/D451>). Patients with a time-weighted average of AT levels less than or equal to less than or equal to 70% were more frequently in post-cardiac arrest condition and had a more severe ICU presentation with a lower Simplified Acute Physiology II score, pH, fibrinogen levels, and platelet count and higher aspartate aminotransferase levels (table 1). Postcardiotomy ECMO was associated with lower AT levels at ECMO initiation with 45% (34 to 55%) compared to nonpostcardiotomy ECMO with 58% (44 to 73%), although the time-weighted average of AT levels was similar (Supplemental Digital Content 2, table S2, <https://links.lww.com/ALN/D451>).

Heparin Responsiveness during Venoarterial ECMO Support

Heparin was initiated early after ECMO initiation, with a median 0 (0 to 10.8) hours. Most patients received subtherapeutic unfractionated heparin dose during the first

Table 1. Baseline Patient, Hematologic, and Surgery Characteristics

Characteristics	All Patients (N = 50)	Time-weighted Average of AT Levels ≤ 70% (N = 32)	Time-weighted Average of AT levels > 70% (N = 18)	P Value
Age, yr	62 (54 to 70)	63 (55 to 70)	60 (53 to 66)	0.240
Female sex	10 (20)	7 (22)	3 (17)	0.730
Body mass index, kg/m ²	25.0 (22.5 to 28.4)	25.3 (21.8 to 29.4)	24.9 (22.9 to 26.2)	0.934
Comorbidities				
Hypertension	19 (38)	10 (31)	9 (50)	0.190
Diabetes	8 (16)	5 (16)	3 (17)	> 0.999
Chronic respiratory disease	1 (2)	1 (3)	0 (0)	> 0.999
Chronic heart failure	10 (20)	8 (25)	2 (11)	0.295
Chronic kidney disease	1 (2)	0 (0)	1 (6)	0.360
Active solid cancer	4 (8)	4 (12)	0 (0)	0.283
Active smoking	11 (22)	5 (16)	6 (33)	0.172
Chronic alcoholism	6 (12)	3 (9)	3 (17)	0.654
Thromboembolic disease	4 (8)	3 (9)	1 (6)	> 0.999
Liver failure	0 (0)	0 (0)	0 (0)	
Nephrotic syndrome	0 (0)	0 (0)	0 (0)	
ECMO indication				
Postcardiotomy	21 (42)	15 (47)	6 (33)	0.352
Myocarditis	3 (6)	1 (3)	2 (11)	0.291
Acute coronary syndrome	11 (22)	8 (25)	3 (17)	0.724
Pulmonary embolism*	2 (4)	2 (6)	0 (0)	0.530
Cardiac arrest	14 (28)	13 (41)	1 (6)	0.008
Others	12 (24)	4 (12)	8 (44)	0.017
Other cardiac assistance				
Intra-aortic balloon pump	12 (24)	5 (16)	7 (39)	0.123
Impella	2 (4)	1 (3)	1 (6)	0.999
Simplified Acute Physiology Score II score	51 (37 to 76)	59 (46 to 80)	36 (29 to 55)	0.003
Survival after venoarterial ECMO score	−4 (−7 to 1)	−4 (−9 to 3)	−2 (−4 to 0)	0.070
Norepinephrine at hour 0	39 (78)	23 (72)	16 (89)	0.287
Dobutamine at hour 0	38 (76)	22 (69)	16 (89)	0.170
Adrenaline at hour 0	18 (36)	14 (44)	4 (22)	0.128
Baseline laboratory parameters (hour 0)				
Antithrombin level, %	51 (40 to 65)	47 (36 to 56)	60 (43 to 78)	0.035
Creatinine, μmol/l	99 (77 to 141)	101 (80 to 164)	94 (75 to 131)	0.795
pH	7.34 (7.21 to 7.44)	7.25 (7.06 to 7.42)	7.41 (7.30 to 7.46)	0.018
Lactate, mmol/l	5.5 (2.5 to 9.1)	5.9 (2.9 to 11.4)	3.0 (2.0 to 8.0)	0.103
Hemoglobin, g/dl	11.2 (8.7 to 13.7)	10.6 (8.8 to 12.8)	12.4 (9.1 to 14.1)	0.352
Platelet count, 10 ⁹ /l	164 (96 to 220)	126 (89 to 210)	195 (163 to 250)	0.036
Fibrinogen, g/l	2.6 (2.1 to 3.6)	2.3 (1.9 to 3.0)	3.7 (2.7 to 4.2)	0.004
Aspartate aminotransferase, IU/l	356 (82 to 584)	500 (333 to 1,510)	127 (43 to 306)	0.004
Bilirubin, μmol/l	15 (10 to 22)	12 (10 to 22)	17 (12 to 22)	0.220

The results are presented as n (%) or median (interquartile range).

*Cardiac arrest secondary to pulmonary embolism.

AT, antithrombin; ECMO, extracorporeal membrane oxygenation.

24 h with a median of 152 (113 to 242) IU · kg^{−1} · day^{−1}, corresponding to low anti-Xa target levels due to high bleeding risk in postcardiotomy setting (Supplemental Digital Content 2, tables S1 and S2, <https://links.lww.com/ALN/D451>). Heparin dosage was stable between days 1 and 7 (301 to 403 IU · kg^{−1} · day^{−1}). The time to reach a first anti-Xa level greater than or equal to 0.3 IU/ml was 13 (5 to 31) hours (table 1). The time spent within anti-Xa target 0.30 to 0.50 IU/ml was only 38% (15 to 56%) of total ECMO time, due to frequent reductions of anti-Xa target related to overt bleeding events (table 2) and to a median of 1 (1 to 2) unfractionated heparin interruption per patient. As an exploratory analysis, the heparin responsiveness index (ratio of unfractionated heparin

dosage to the anti-Xa level at each time point) exhibited high variability between patients and time points, without displaying a distinct pattern during the course of ECMO support (Supplemental Digital Content 2, fig. S3, <https://links.lww.com/ALN/D451>). The use of unfractionated heparin bolus in our protocol was not associated with heparin overdose, with 0% (0 to 4%) of ECMO time above anti-Xa greater than 0.70 IU/ml (table 2).

Relationship between Heparin Responsiveness and AT Levels

Patients with a time-weighted average of AT levels less than or equal to 70% did not demonstrate decreased heparin

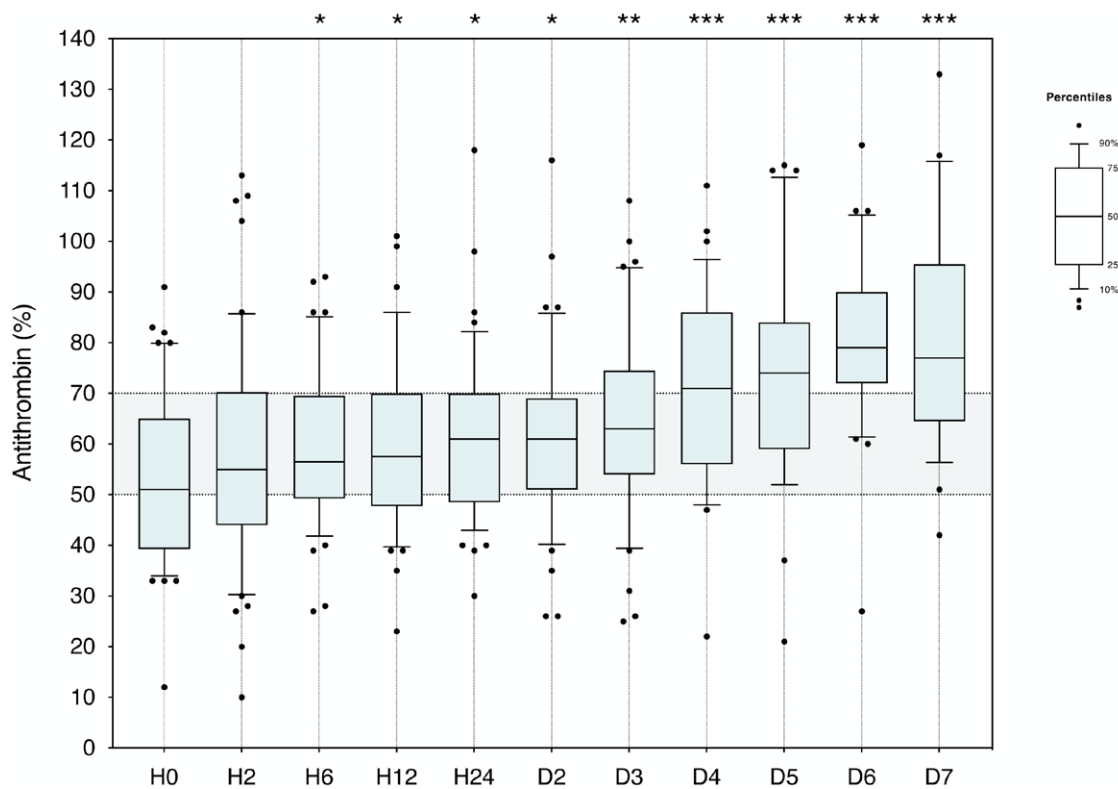


Fig. 2. Antithrombin (AT) plasma levels changes during the first 7 days of venoarterial extracorporeal membrane oxygenation (ECMO) support. *P* values are for multiple comparisons with baseline AT levels: **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

responsiveness, as evidence by a short time to achieve a first anti-Xa activity greater than 0.30 IU/ml with 12 (5 to 38) hours as compared to patients with time-weighted average greater than 70% with 15 (4 to 28) hours (table 2; *P* = 0.990). In the same way, the percentage of ECMO time spent in the 0.30 to 0.50 anti-Xa range was not significantly different according to time-weighted averages of AT levels, with 39% (13 to 50%) and 32% (23 to 60%) for time-weighted average less than or equal to 70% and greater than 70%, respectively (table 2). However, patients with a time-weighted average of AT levels greater than 70% spent significantly more of their ECMO time above an anti-Xa level of 0.50 IU/ml, with 10% (5 to 19%) of ECMO time (table 2; *P* = 0.042). The relationship between heparin responsiveness and AT levels during the first 7 days of ECMO is depicted in figure 4. AT levels were not correlated to anti-Xa activity (Spearman $r = 0.03$; *P* = 0.660) and demonstrated a weak correlation with unfractionated heparin dosage ($r = 0.26$; *P* = 0.009). Further, the heparin responsiveness index was not correlated to AT levels ($r = 0.04$; *P* = 0.570).

Bleeding and Thrombotic Complications

Overall, 36 (72%) patients suffered from 70 bleeding events—irrespective of severity—during total ECMO

support, with cannulation site being the most frequent bleeding type (20%). Intracranial hemorrhage accounted for 4.6% of total events (three events in three patients). Postcardiotomy ECMO was associated with a high bleeding incidence of 90% (Supplemental Digital Content 2, table S2, <https://links.lww.com/ALN/D451>). Bleeding patients had a higher time-weighted average of AT levels compared to nonbleeding patients with 69% (59 to 79%) and 57% (46 to 62%), respectively (Supplemental Digital Content 2, table S3, <https://links.lww.com/ALN/D451>; *P* = 0.004). Despite a higher number of unfractionated heparin interruption, the time spent within anti-Xa target 0.30 to 0.50 IU/ml was not different between bleeding and nonbleeding patients (supplemental table S3, <https://links.lww.com/ALN/D451>). The number of erythrocyte transfusions was not significantly different based on the time-weighted average of AT levels, with a median of 3 (2 to 8) units *versus* 5 (3 to 10) units (*P* = 0.328), respectively, for the groups with a time-weighted average less than or equal to 70% and greater than 70%. The same results were observed for fresh frozen plasma, with 1 (0 to 4) units *versus* 0 (0 to 6) units (*P* = 0.939), and for platelet concentrates with 0 (0 to 2) units in both groups (*P* = 0.690). A total of 23 patients (48%, *n* = 48 patients without HIT) experienced

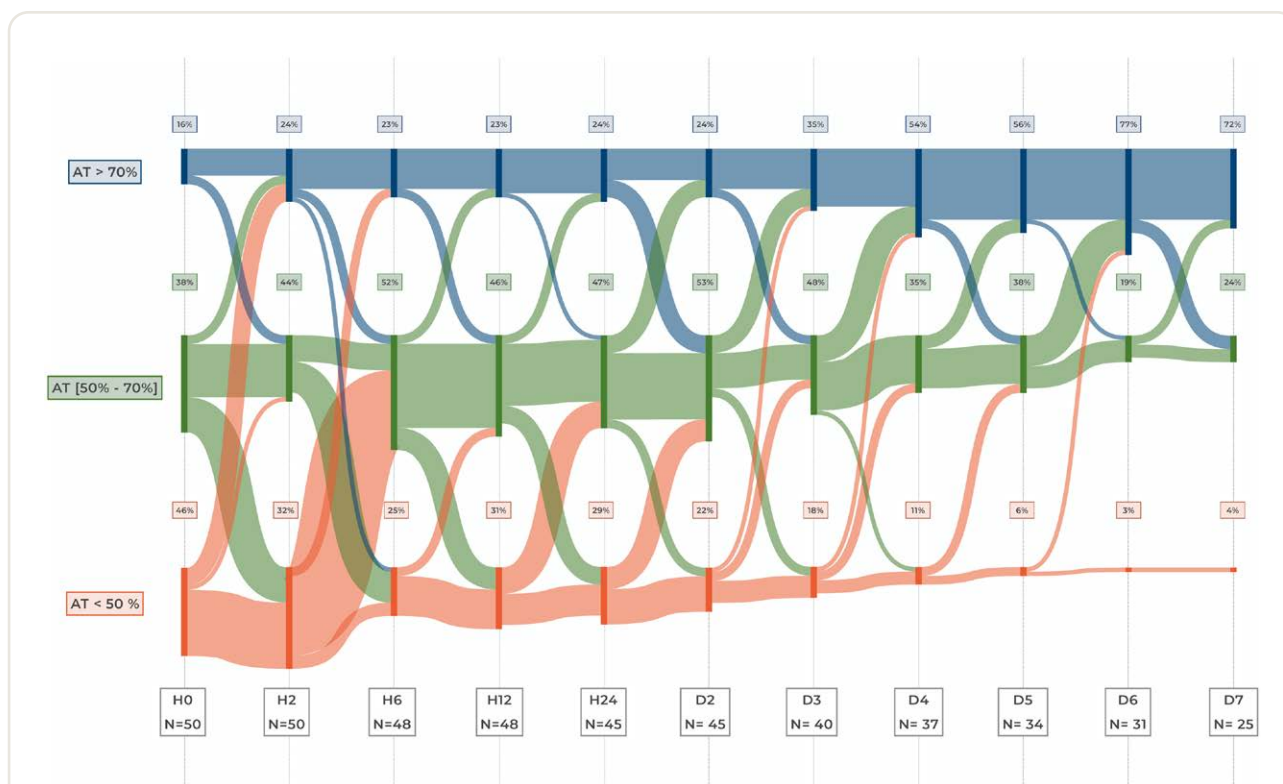


Fig. 3. Antithrombin (AT) plasma levels changes according to the extent of AT deficiency. For each time point (hours 0 to 24 and days 2 to 7), discrete AT levels were defined as follows: normal values above 70%, moderate deficiency between 50% and 70%, and severe deficiency less than 50%. The number of patients is shown under each time point.

Table 2. Heparin Responsiveness according to Time-weighted Average of AT Levels during Venous Arterial ECMO Support

Characteristics	All Patients (N = 50)	Time-weighted Average of AT Levels ≤ 70% (N = 32)	Time-weighted Average of AT Levels > 70% (N = 18)	P Value
Time to reach first anti-Xa ≥ 0.30 IU/ml (hours)*	13 (5–31)	12 (5–38)	15 (4–28)	0.990
ECMO time spent in anti-Xa range*, %				
Anti-Xa < 0.30 IU/ml	50 (31–74)	55 (34–78)	34 (29–64)	0.148
Anti-Xa [0.30–0.50] IU/ml	38 (16–55)	39 (13–50)	32 (23–60)	0.326
Anti-Xa > 0.50 IU/ml	6 (2–16)	5 (0–13)	10 (5–19)	0.042
Anti-Xa > 0.70 IU/ml	0 (0–4)	0 (0–4)	0 (0–4)	0.596
Number of unfractionated heparin interruptions	1 (1–2)	1 (0–2)	1 (1–2)	0.226

The results are presented as medians (25th to 75th percentile).

*Calculated based on all anti-Xa performed as routine care for unfractionated heparin anticoagulation monitoring during ECMO support.

AT, antithrombin; ECMO, extracorporeal membrane oxygenation.

at least one thrombotic event (0.8 thrombotic events per patient). Device-related thrombosis, including macroscopic clotting of circuit and/or membrane, oxygenator failure, and acute circuit thrombosis, accounted for most thrombotic events. Ischemic stroke was diagnosed in five patients (seven events). No relationship between thrombotic events and either AT or anti-Xa levels was found (Supplemental Digital Content 2, table S4, <https://links.lww.com/ALN/D451>).

Discussion

Our study reports extensive data regarding AT levels and heparin responsiveness during the first 7 days of venous arterial ECMO support. The main findings were as follows. First, moderate acquired AT deficiency was frequent and significantly improved over the course of ECMO support, particularly after the initial 72h after venous arterial ECMO initiation. Second, the use of a weight-based heparin

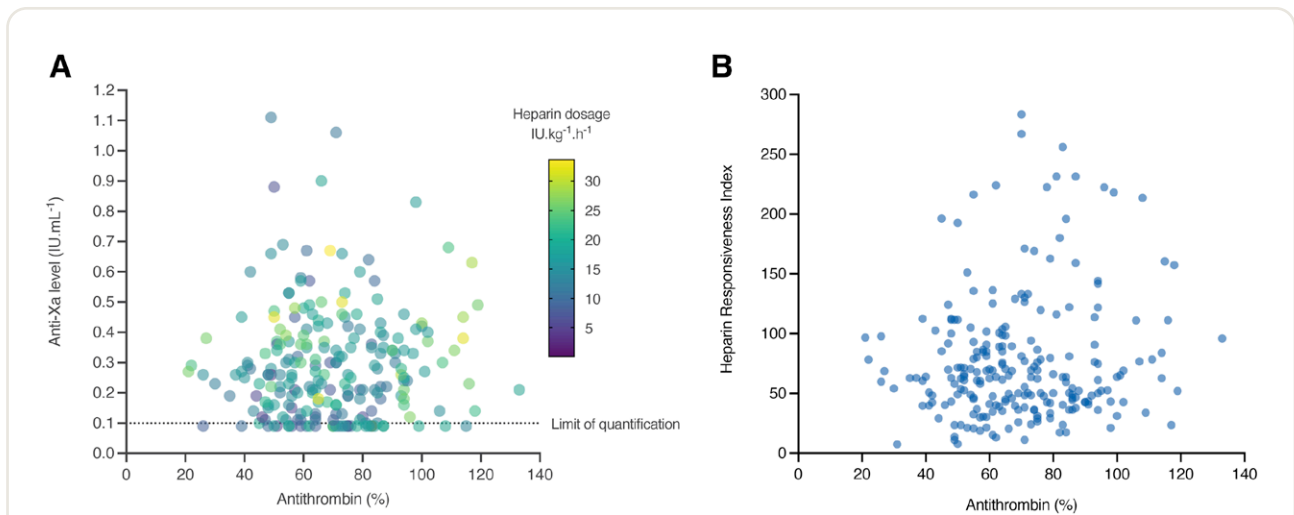


Fig. 4. Relationship between antithrombin and heparin responsiveness. (A) Relationship between antithrombin, anti-Xa levels, and heparin dosage. (B) Relationship between antithrombin levels and the heparin responsiveness index. The heparin responsiveness index is defined as unfractionated heparin dosage ($\text{IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$)/anti-Xa level (IU/ml). The values at hours 0, 2, and 6 were removed to avoid any residual effect from possible unfractionated heparin administration before the start of the study.

protocol with boluses and continuous infusion was associated with a rapid achievement of the target anti-Xa levels after the initiation of heparin. Third, AT levels were not correlated with heparin responsiveness, as assessed by the concurrent measurement of heparin dosage and its effect on anti-Xa levels at each time point.

We found slightly higher AT levels than previously reported during adult venoarterial ECMO support.^{19–21} This might be explained by the lower frequency of post-cardiac arrest ECMO, associated in our cohort with a lower time-weighted average of AT levels. Conversely, AT levels were lower compared to published data on venovenous ECMO.^{3,18,19} Finally, the progressive increase in AT levels over time on venoarterial ECMO was consistent with previously reported results by Mazzeffi *et al.*²⁰ but not with those reported by Cartwright *et al.*¹⁹ Our study was not designed to address the mechanisms underlying this correction in AT levels. However, we can hypothesize that it may be due to a decrease in consumption with the resolution of shock, as well as an increase in production accompanying the correction of any potential hepatic failure associated with the initial shock.

While data showed that heparin responsiveness during cardiopulmonary bypass was not always dependent on AT levels,^{29,30} interventional studies have demonstrated an increase in activated coagulation time after AT supplementation, although without benefit on clinical outcomes.^{31–34} Following these findings, the use of AT supplementation has increased in both adult and pediatric ECMO to enhance anticoagulation.^{3,9,22,31,34} However, data on unfractionated heparin management during cardiopulmonary bypass cannot be easily extrapolated to ECMO support due to its prolonged duration, associated organ failures, and

the delicate thrombosis/bleeding balance. Indeed, only one small trial has assessed AT supplementation in venovenous ECMO without positive outcomes, and no evidence exists for venoarterial ECMO.¹⁸ Moreover, the exact AT plasma level needed for effective heparin anticoagulation remains unclear, but some suggest that 50 to 60% of AT might sustain the heparin response measured with an anti-Xa.³⁵

Our study showed no correlation between heparin responsiveness, as monitored using an anti-Xa assay without added AT or dextran, and AT levels. Due to high variability in the response to unfractionated heparin, using either unfractionated heparin dosage or anti-Xa alone does not accurately assess heparin responsiveness. As an exploratory analysis, we evaluated a heparin responsiveness index, defined for each anti-Xa measurement as the ratio of unfractionated heparin dosage ($\text{IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) to the anti-Xa level (IU/ml). Compared to previously developed index for cardiopulmonary bypass (heparin sensitivity index),^{10,27,28} this index facilitates a concurrent and dynamic assessment of both heparin dosage and its corresponding anti-Xa with each adjustment in dosage. This study was not designed to validate this index against clinical outcomes, which will require future prospective validation. Overall, our results do not advocate for AT supplementation aiming at either increasing anti-Xa levels and/or decreasing unfractionated heparin dosage during venoarterial ECMO support.

Decreased heparin responsiveness, also referred to as heparin resistance, is well documented during cardiopulmonary bypass with unfractionated heparin monitored using activated coagulation time, but its frequency during ECMO is debated.^{9,11,34} This inconsistency likely arises from the lack of an established heparin responsiveness definition and the high heterogeneity in unfractionated heparin dosing and

monitoring practices across centers.³ In our study, the use of a weight-based dosing protocol, which includes a bolus at the initiation of unfractionated heparin, a high starting dosage ($18 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), and boluses with dose increments, allowed us to quickly achieve therapeutic anti-Xa targets greater than or equal to 0.30. However, despite targeting an anti-Xa level of 0.30 to 0.50 IU/ml using the weight-based nomogram, time within the therapeutic range was limited because of frequent bleeding events necessitating unfractionated heparin dose adjustments or halts. This highlights once again the challenge of managing ECMO patients with high bleeding and thrombosis risk.

Beyond heparin responsiveness, AT supplementation has been considered to mitigate systemic inflammation and organ damage.³⁶ Previous studies on its effects in severe sepsis found no benefits or bleeding risks.³⁷ Similarly, a recent placebo-controlled trial of preoperative AT supplementation in cardiac surgery failed to demonstrate an improvement in adverse postoperative outcomes.³⁸ In our study, the time-weighted average of AT levels was higher in bleeding patients aligning with reports linking elevated AT levels to increased postoperative bleeding after cardiac surgery and during ECMO.^{33,39,40} However, our study was not designed to assess the direct link between AT levels and bleeding or thrombotic events, and it was not feasible to account for the various confounding factors and competitive risks necessary for causal inference. Future research should evaluate the efficacy and safety of AT supplementation during ECMO support.

Our study has several strengths. First, it provides a longitudinal analysis of both AT levels and laboratory heparin responsiveness measured by anti-Xa, extending up to 7 days after the initiation of venoarterial ECMO. Second, we used a multidimensional approach to heparin responsiveness, which combines unfractionated heparin dosage and anti-Xa levels at each dosage adjustment, and time spent in the therapeutic anti-Xa range. Third, anticoagulation was consistently managed through a weight-based protocol including boluses at initiation and with each dosage increase. Finally, our approach to anticoagulation on ECMO is in full agreement with the guidelines issued later by the Extracorporeal Life Support Organization and the International Society on Thrombosis and Haemostasis.^{4,5}

Our study has several limitations. First, this study evaluates the impact of AT levels on the response to heparin as measured by anti-Xa without the addition of AT or dextran. Consequently, its generalizability to other heparin dosage protocols or monitoring methods cannot be guaranteed. Second, this study was not designed to address the choice of monitoring between activated PTT and anti-Xa. Third, the moderate AT deficit observed does not allow us to draw conclusions for very severe deficit situations of less than or equal to 20%, which were scarcely represented in our cohort. Fourth, the small sample size precluded us from drawing conclusions regarding the impact of AT levels on thrombosis and bleeding events. Fifth, although we excluded

patients with known inherited AT deficiency, we did not test for heparin binding site AT deficiency. However, given the rarity of type II AT deficiencies, it is highly unlikely that any of our patients had such deficiency. Finally, the heparin responsiveness index was introduced as an exploratory tool and lacks prospective validation against clinical outcomes.

Conclusions

In this single-center prospective cohort study including 50 patients, venoarterial ECMO support was associated with decreased AT levels that significantly improved over the course of ECMO support, particularly after the initial 72h after venoarterial ECMO initiation. These AT levels did not correlate with heparin responsiveness, as monitored using an anti-Xa level without addition of dextran or AT, as part of a weight-based heparin protocol. Our study does not support the routine measurement of AT levels and its supplementation to enhance heparin responsiveness during venoarterial ECMO support. This highlights the need for prospective interventional studies on anticoagulation during ECMO and challenges the concept of decreased heparin responsiveness.

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Competing Interests

Dr. Mansour received payments made to his institution from i-SEP (Nantes, France) for consulting fees, and from French Fractionating and Biotechnologies Laboratory (Les Ulis, France), Aguettant (Lyon, France), Viatrix (Lyon, France), and Pfizer (Paris, France) for lecture fees. The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Digital Content 1. Unfractionated heparin dosage protocol during venoarterial ECMO support, <https://links.lww.com/ALN/D450>
Supplemental Digital Content 2. Supplementary tables and figures, <https://links.lww.com/ALN/D451>

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