ORIGINAL ARTICLE

Comparison of Prophylactic and Therapeutic Doses of Anticoagulation for Acute Chest Syndrome in Sickle Cell Disease

The TASC Double-Blind Controlled Randomized Clinical Trial

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Abstract

Rationale: Patients with sickle cell disease hospitalized for acute chest syndrome (ACS) are at high risk of *in situ* pulmonary microthrombosis.

Objectives : We evaluated whether therapeutic anticoagulation could shorten ACS duration.

Methods: TASC (Therapeutic Anticoagulation for Acute Chest Syndrome in Sickle Cell Disease) is a randomized, controlled, double-blind trial conducted in 12 French hospitals (December 2016–April 2021) in adult patients with ACS with no initial thrombosis on chest computed tomography with pulmonary angiogram. We randomized 172 patients (1:1) to receive either prophylactic or therapeutic doses of low-molecular-weight tinzaparin for 7 days. The primary efficacy outcome was time to ACS resolution. The primary safety outcome was major bleeding. Main secondary outcomes included parenteral opioid consumption, transfusion, mortality at hospital discharge, and hospital readmissions at 6 months.

Measurements and Main Results: The primary efficacy outcome, time to ACS resolution, analyzed using a Cox model, was shorter with therapeutic anticoagulation than with prophylactic doses (hazard ratio, 0.71; 95% confidence interval, 0.51 to 0.99; $P = 0.044$). As a supplemental estimate, the restricted mean time to ACS resolution (over a 15-d horizon or discharge) was shorter with therapeutic doses (4.8 ± 0.4 vs. 6.1 ± 0.5 d). The primary safety outcome (major bleeding) did not occur in either group. The cumulative dose of parenteral opioids was lower with therapeutic anticoagulation: median [interquartile range] of 124 [80 to 272] vs. 219 [65 to 378] mg morphine equivalent; difference, −96; 95% confidence interval, −202 to −46; $P = 0.02$. Other short- and long-term secondary outcomes were similar between groups.

Conclusions: In adult patients with ACS, a therapeutic anticoagulation shortened ACS duration and reduced opioid consumption compared with prophylactic doses, without increasing bleeding risk.

Clinical trial registered with www.clinicaltrials.gov (NCT02580773).

Keywords: anticoagulation; tinzaparin; sickle cell disease; acute chet syndrome

(Received in original form September 9, 2024; accepted in final form March 14, 2025)

Am J Respir Crit Care Med Vol 211, Iss 5, pp 832–841, May 2025

Originally Published in Press as DOI: 10.1164/rccm.202409-1727OC on March 14, 2025
Internet address: www.atsjournals.org

Sickle cell disease (SCD) is one of the most common monogenic diseases worldwide, and typically half of its sufferers experience acute chest syndrome (ACS) during their lifetime (1). ACS is the most common reason for critical care admission in SCD (2–4), where patients often require acute organ support, especially mechanical ventilation (5–7). It is considered one of the leading causes of death from SCD, especially in adulthood (8–10).

From a pathophysiological point of view, ACS is a condition often associated with severe pulmonary vascular dysfunction (5) characterized by constriction and obstruction of pulmonary vessels. Approximately 16% of ACS episodes are attributed to pulmonary infarction resulting from local vasoocclusion (7). A previous study explored large elastic vessels of >1 mm in diameter using chest computed tomography with pulmonary angiogram (CTPA) and showed the presence of pulmonary artery thrombosis in about 17% of ACS episodes in adults (11). These macrothromboses, which were mainly of fibrinocruoric rather than fatty composition (11), indicate therapeutic anticoagulation in routine clinical practice (12). The hypothesis that these pulmonary thromboses are formed *in situ* is suggested by their peripheral distribution in the lung vasculature and the low prevalence of concomitant deep venous thrombosis (11). It is therefore likely that they represent the visible part of a wider thrombotic process involving pulmonary microvessels in the majority of patients. High-resolution CT scans often show paucity or absence of contrast enhancement in the lungs' small vessels, arterioles, and venules of patients with ACS (13), and *in situ* microthromboses are found on top of macrothromboses at autopsy (14–16). It is possible that vasoocclusion is exacerbated in a prothrombotic milieu driven by dysregulated hemolysis. Whether therapeutic anticoagulation can hasten ACS resolution by alleviating pulmonary microthrombosis or not is still unknown.

To address this uncertainty, we designed a randomized controlled trial in patients with ACS who had no macrovascular thrombosis on initial CTPA to compare prophylactic with therapeutic dose anticoagulation. Our primary hypothesis was that the latter decreases disease duration compared with the former, without increasing major bleeding. Our secondary objective was to compare the two strategies in terms of nonmajor bleeding, morbidity (transfusion, morphine, and organ support needs), and long-term outcomes (hospital readmission, ACS recurrence, and death).

Methods

Study Design and Protocol

The TASC (Therapeutic Anticoagulation for Acute Chest Syndrome in Sickle Cell Disease) trial was a double-blind, multicenter, randomized controlled trial that enrolled patients with SCD affected by ACS and treated in 12 health centers in France from December 16, 2016 to February 2, 2021 (details on the health centers are shown in the online supplement). A central institutional ethics review board (Comité de Protection des Personnes, Ile-de-France V, Paris, France) approved this trial (no. 15076-AOR14068-P140305-TASC-EUD2015-00107-45) in accordance with the Declaration of Helsinki. Each patient or next of kin provided written informed consent before inclusion (*see* Methods E1 in the online supplement). This study followed the Consolidated Standards of Reporting Trials reporting guideline.

Study Sample

All consecutive adult (≥18 yr) patients with SCD (SS, SC, $S\beta^0$, or $S\beta^+$ thal genotypes), hospitalized for newly diagnosed ACS, were eligible for inclusion. ACS was defined by a new pulmonary parenchymal infiltrate in at least one segment on chest X-ray or CT scan together with a respiratory symptom (chest pain, dyspnea, or cough) or a pulmonary auscultation anomaly (crepitation, tubular breath sounds, or decreased vesicular breath sounds) (12). Main exclusion criteria included ACS diagnosis since >48 hours, body weight <40 kg or >100 kg, a calculated creatinine clearance rate of <60 ml/min, clinical indication for therapeutic anticoagulation, contraindications to therapeutic anticoagulation, and if red blood cell transfusion was deemed highly risky. The full list of eligibility criteria is available in Methods E2.

Randomization and Masking

As per the trial protocol, CTPA had to be performed within 72 hours before or up to 24 hours after inclusion (*see* Figure E1 in the online supplement). If the CTPA did not show pulmonary artery thrombosis, the

Supported by Assistance Publique–Hôpitaux de Paris and LEO Pharma (Ballerup, Denmark). LEO Pharma 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.

Author Contributions: A.M.D. and B.M. had full access to all the data of the study and both take responsibility for the integrity of the data and the accuracy of their analyses. A.M.D. and B.M. conceived the trial and wrote the initial proposal. S.K. wrote the statistical analysis plan and estimated the sample size. A.M.D., A.H., J.-B.A., M.F., L.G., L.A., S.N., J.O., B.C., M.L.-S., G.M., M.E.-J., I.D., F.L., G.L., D.R., C.G., M.M., P.B., D.D.S., K.R., A.C.-N., S.G., S.K., and B.M. collected the data. A.M.D. and B.M. vouch for the data and their analyses and for the compliance of this report with the study protocol and data analysis plan. S.K., A.C.-N., and S.G. had access to the study data and did the statistical analyses. The manuscript, as well as its various drafts, were revised by all authors to validate its intellectual content. All co-authors have approved the final version of the manuscript and agreed to submit the present version, to be accountable for all aspects of the work, and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing: The trial steering committee will work to make study data available on legitimate request. Notwithstanding, the steering committee must grant that any proposed publication should be of high quality, respect the commitments the study participants agreed on in the consent forms and ethical approvals, and fulfill the related legal and regulatory requirements (e.g., concerning data protection and privacy). The steering committee has the right to review and comment on any draft manuscript before publication.

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

At a Glance Summary

Scientific Knowledge on the Subject: Observational studies suggest that *in situ* pulmonary microthrombosis is an important factor in the pathophysiology of acute chest syndrome (ACS). We conducted a PubMed search on September 1, 2024 using the terms "acute chest syndrome", "sickle cell", and "anticoagulation", with no restrictions on language or date, to identify relevant studies. Our search identified only one single-center, open-label pilot feasibility trial that evaluated the effects of unfractionated heparin in ACS. This trial did not meet its prespecified feasibility criteria and was terminated early because of poor recruitment, with only seven patients randomized over 4 years, preventing any in-depth analysis.

What this Study Adds to the Field: To our knowledge, this is the first phase 3 randomized clinical trial to evaluate therapeutic anticoagulation during ACS. Administering therapeutic doses of low-molecular-weight heparin tinzaparin for 7 days improved the efficacy criterion of reducing the duration of ACS without increasing the risk of bleeding compared with prophylactic doses. The cumulative dose of parenteral opioids was lower with therapeutic-dose anticoagulation than it was with prophylactic-dose anticoagulation. This study is the first to demonstrate that a drug can shorten the duration of ACS in sickle cell disease.

patient was randomized to one of the two anticoagulation regimens. Centralized 1:1 ratio block randomization using random block sizes of 4 was stratified by hospital and according to hypoxemia at inclusion (i.e., a ratio of Pa_{O_2} to FI_{O_2} of $<$300 mm Hg) (17).

Trial Interventions

Immediately after randomization, patients were put on prophylactic (4,500 IU/24 h) or therapeutic (175 IU/kg/24 h) dose of low-molecular-weight tinzaparin for 7 days, or until hospital discharge, whichever came first. *See* Methods E2 for details of tinzaparin administration blinded to participants, care providers, and those assessing outcomes. In the two groups, the trial anticoagulant was discontinued when a patient developed severe kidney failure (creatinine clearance $<$ 30 ml/min) or serious anticoagulation-related adverse events, required a procedure, or presented a clinical condition at high risk of bleeding, and when therapeutic anticoagulation was clinically indicated (Methods E2) (18). Patient compliance was defined as adherence to assigned treatment for $\geqslant$75% of the time recommended by the protocol or until occurrence of major bleeding, death, or hospital discharge, whichever occurred first. In both groups, current recommendations for the management of ACS were followed, including hydration, pain control, transfusion (based on predefined criteria), antibiotics, oxygen therapy, and respiratory support if needed (Methods E2) (19, 20).

Primary and Secondary Outcomes

Complete definitions of study outcomes are available in Methods E3. The primary efficacy outcome was the time (days) to ACS resolution, defined as the time from randomization to the joint improvement of four criteria, including fever, chest pain, dyspnea, and hypoxemia. For nonhypoxemic patients, only the first three criteria were considered. The primary safety outcome was the rate of major bleeding. The definition of major bleeding was adapted from International Society on Thrombosis and Hemostasis (21) and Randomized Evaluation of Long-Term Anticoagulation Therapy definitions (22) but excluded transfusion requirement, which is a routine treatment of severe vasoocclusive crisis (VOC) and ACS (19, 20). The secondary outcomes at hospital discharge included nonmajor bleeding, the need for (and volume of) transfusion and phlebotomy, the need for mechanical ventilation, catecholamine infusion, the cumulative dose of parenteral opioids, ICU admission, length of hospital stay, and all-cause death. The secondary outcomes at 6 months included hospital readmissions, thrombotic events, and all-cause death.

Statistical Analysis

Sample size calculation for the primary efficacy endpoint (time to ACS resolution) and all statistical analyses, including those used to compare secondary outcomes, are detailed in Methods E4. We aimed to include 200 patients so that 172 (86 per group) could be randomized.

Primary endpoint analyses were performed according to randomization group on an intention-to-treat basis, and additional supportive analyses were performed on the per-protocol population who did not deviate from the protocol, as defined in eMethods 4. For the primary efficacy endpoint analysis, cumulative event curves (censored endpoints) were estimated for time to ACS resolution with the Kaplan-Meier procedure up to Day 15 or hospital discharge, whichever came first. Because no deaths were observed during the study period, adjustments for informative censoring related to death were not required. The association between randomization group and ACS resolution was compared using a Cox model analysis stratified by hypoxemia at inclusion and was reported as hazard ratio (HR) with its 95% confidence interval (CI). An HR $<$1 indicates a shorter time to ACS resolution with therapeutic-dose anticoagulation, whereas an HR $>$1 would indicate a longer time. To account for stratified randomization, a marginal Cox model was used to address intrasite correlation by clustering on the inclusion site. This approach adjusts standard errors and *P* values for potential site-level effects without requiring the estimation of fixed effects for each site, making it particularly suitable for centers with a small number of patients. In addition, a frailty Cox model was used, incorporating a random effect for sites. Risk proportionality was assessed using the Schoenfeld test. Information on the primary endpoint was complete for the intention-to-treat analysis, whereas analyses of secondary endpoints were performed on a complete cases basis, with no imputation of missing information. The restricted mean survival time was computed using the rmst2 function from the survRM2 package in R and expressed as mean value $\pm$ SE.

All analyses were performed according to a predefined statistical analysis plan, using Stata v16.1 (StataCorp) and R 4.0.3 (R Foundation for Statistical Computing). Statistical tests were two-tailed, and *P* values of $<$0.05 were considered statistically significant. Data analyses were performed from August 23, 2022 to August 30, 2023.

Results

Patients and Intervention

From December 16, 2016 to February 2, 2021, a total of 573 patients were screened, of

whom 198 patients (mean [SD] age, 29.9 [8.7] yr; 114 [58%] men and 84 [42%] women; race and ethnicity information were not collected as per French law) were included and 375 were excluded (ineligible). Of the 198 included patients, 195 underwent CTPA (2 randomization failures and 1 patient withdrew consent and declined further participation before randomization). Prerandomization CTPA detected pulmonary artery thrombosis in 22 patients and was nonconclusive in one patient (Figure 1). Eventually, 172 patients were randomized to receive the therapeutic ($n = 88$) or prophylactic ($n = 84$) dose of anticoagulation.

Of the 172 patients randomized, 4 were removed from the main analysis for early consent withdrawal ($n = 1$) or violation of eligibility criteria ($n = 3$); the remaining 168 patients formed the intention-to-treat population (Table 1), and most had the SS genotype (Table E1). The median (interquartile range) time from ACS diagnosis to randomization was 1 (1–1) day (Table 1). The main events associated with ACS were VOC and infection (Tables 1 and E2). At randomization, 63 (37.5%) of the enrolled patients were hypoxemic (Table 1). Characteristics at baseline (Table E1) and at inclusion (Table 1) showed no clinically relevant difference between groups. Patients' compliance was high in both groups (77/86 and 80/82 patients in the therapeutic and prophylactic anticoagulation dose, respectively; $P = 0.10$; Table E3).

Primary Efficacy and Safety Outcomes

The primary efficacy outcome—time to ACS resolution—analyzed using a Cox model was shorter with therapeutic-dose anticoagulation than with prophylactic-dose anticoagulation (HR, 0.71; 95% CI, 0.51–0.99; $P = 0.044$) (Table 2 and Figure 2). The Schoenfeld test confirmed that the proportional hazards assumption was satisfied for the overall model ($P = 0.99$), as well as for randomization ($P = 0.94$) and stratification ($P = 0.93$) (Figure E2). As a supplemental estimate, the restricted mean time to ACS resolution (over a 15-d horizon or until discharge, whichever occurred first) was shorter with therapeutic-dose anticoagulation than with prophylactic-dose (4.8 ± 0.4 vs. 6.1 ± 0.5 d). The rate of ACS resolution within 15 days of randomization was 67/82 (81.7%) in patients receiving the prophylactic-dose anticoagulant and 75/86 (87.2%) in patients receiving the therapeutic-dose anticoagulant. The primary safety outcome—major bleeding—did not occur in either group (Table 2).

Secondary Outcomes

The cumulative dose of parenteral opioids was lower with a therapeutic dose of anticoagulation than with a prophylactic dose (124 [80 to 272] vs. 219 [65 to 378] mg of morphine equivalent; difference, −96; 95% CI, −202 to −46; $P = 0.02$; Table 2). All other secondary outcomes at hospital discharge were similar between groups, including the rate of nonmajor bleeding, the need and volume of transfusion and phlebotomy, the need for respiratory support, or catecholamine infusion (Table 2). The secondary outcomes at 6 months (hospital readmissions, thrombotic events, and all-cause deaths) were also similar between groups (Table 2).

Subgroup and Sensitivity Analyses

The results of the primary efficacy outcome were comparable when analyzed using either a marginal Cox model clustering on the inclusion site (HR, 0.71; 95% CI, 0.53–0.94; $P = 0.019$) or a frailty Cox model incorporating random effects for sites (HR, 0.71; 95% CI, 0.50–0.98; $P = 0.041$), with a negligible frailty variance (5×10^{-9}), suggesting minimal site-level effects. The resolution of ACS was mainly driven by the improvement of fever, chest pain, and dyspnea (Figure E3). Subgroup analyses supported the findings of the main analysis of the primary efficacy outcome, showing no significant interaction between the treatment group and genotype (prespecified analysis), hypoxemia (prespecified analysis), patient location (ICU or ward) before inclusion (*post hoc* analysis), or the clinical severity score of Hebbel and colleagues (24) as modified by Lee and colleagues (25) (*post hoc* analysis), as detailed in Figure 3. These results suggest that the treatment effect was homogeneous across these subgroups. However, in most subgroups, the HR for the primary endpoint did not reach statistical significance, likely because of the limited sample size and reduced statistical power. Findings of the per-protocol analysis were similar to those of the intention-to-treat analysis (Figure 3 and Table E4).

Discussion

We compared two regimens of anticoagulation in patients with SCD presenting with ACS and observed that a 7-day course of therapeutic-dose anticoagulation improved the primary efficacy criterion of time to ACS resolution, with no increase in bleeding, compared with prophylactic-dose anticoagulation. In addition, patients in the therapeutic-dose anticoagulation group used significantly less cumulative dose of parenteral opioids than those in the prophylactic-dose anticoagulation group. All other short-term and long-term secondary outcomes were similar between groups.

Currently, there are limited SCD-specific treatments available on the market. The U.S. Food and Drug Administration has approved four drugs for the treatment of SCD: L-glutamine, hydroxyurea, voxelotor, and crizanlizumab. Among these, only hydroxyurea and voxelotor received approval in European countries. However, voxelotor was recently withdrawn from global markets because of safety concerns, including an increased risk of VOCs and potential mortality (26). Some of these medications have the potential to decrease the incidence rate of acute complications associated with SCD, as documented by various studies (27–30). However, it is important to note that currently no therapeutic intervention has demonstrated efficacy in mitigating the effects of VOC (31, 32) or ACS (33) once they have settled. The current approach to treating ACS primarily relies on supportive measures. Our trial is the first to demonstrate that a medication can shorten the duration of this complication.

Pulmonary artery pressure may increase in ACS, and this increase is often associated with a simultaneous increase in cardiac biomarkers, as well as the risk of death (5). Acute right heart failure is a common finding in almost all deaths of patients with SCD admitted to the ICU (4). Moreover, all patients with SCD who developed moderate-to-severe acute respiratory distress syndrome secondary to ACS experienced pulmonary vascular dysfunction, and >80% of them exhibited acute cor pulmonale (34). The frequent occurrence of acute cor pulmonale in this context (5) may contribute to circulatory shock and multiorgan failure (35, 36). The two main drivers of pulmonary vascular dysfunction during ACS are vasoconstriction and vasoocclusion. For the former, high-dose nitric oxide was not proven better in lowering the rate of treatment failure in a randomized trial of

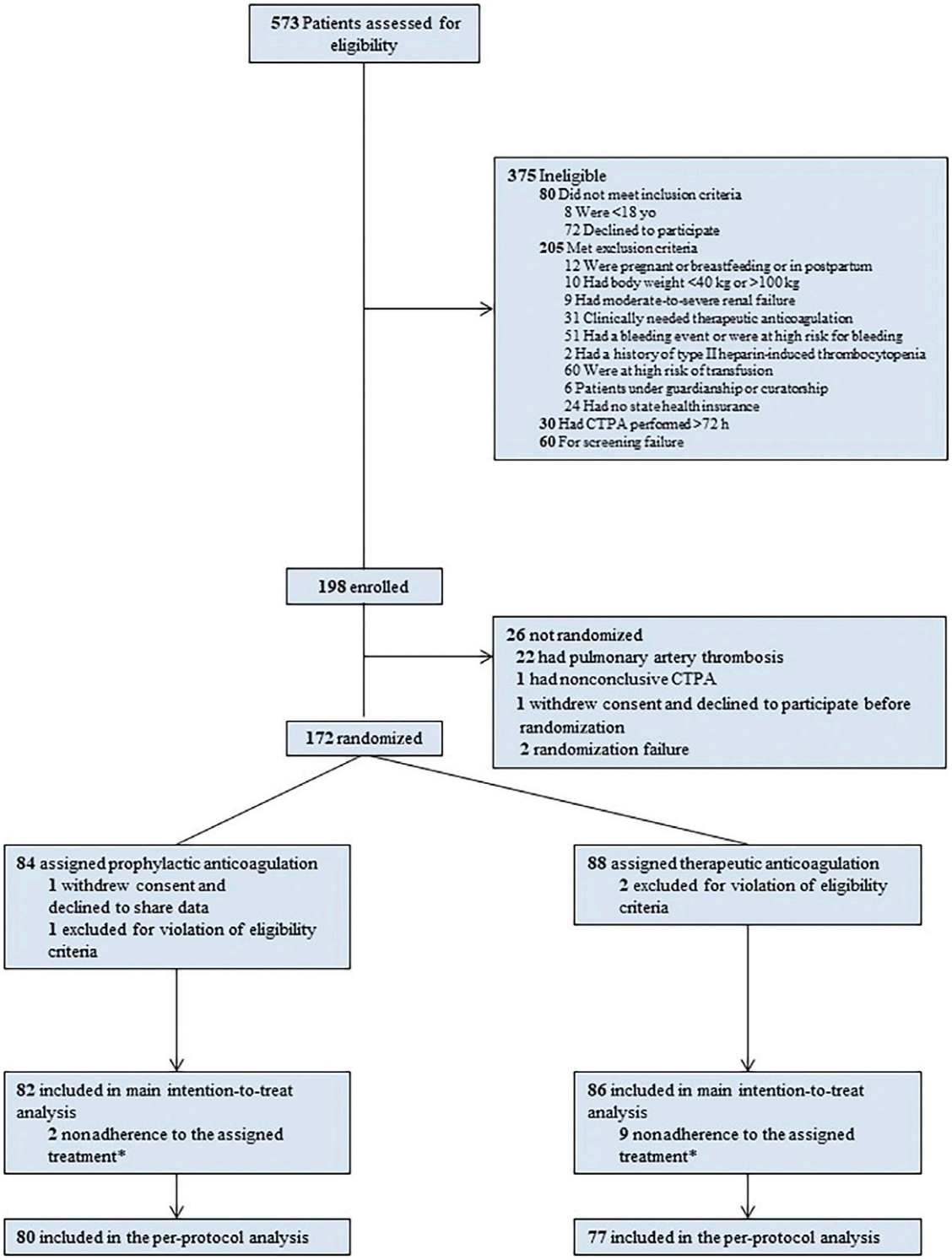

Figure 1. Study flow chart. *Defined as spending <75% of time on assigned treatment from randomization to Day 7 (or until reaching major bleeding or hospital discharge, whichever comes first). CTPA = computed tomography with pulmonary angiogram.

adult patients with SCD presenting mild-to-moderate ACS (33). For the latter, two main causes are suspected: fat embolism (37), which is not amenable to a specific treatment to date, and *in situ* fibrinocruoric thrombosis, which may be blunted by therapeutic anticoagulation (11, 38). Our research corroborates the detection of pulmonary macrothrombosis in at least 10% of adult patients with newly diagnosed ACS. Furthermore, it highlights the potential significance of *in situ* microthromboses;

Table 1. Characteristics at Inclusion of Study Participants by Treatment Group

	Prophylactic Anticoagulation ($n = 82$)	Therapeutic Anticoagulation ($n = 86$)
Events associated with ACS, *n*/*N* (%)		
Vasoocclusive crisis	67/81 (83)	63/84 (75)
Recent surgery	0	1/82 (1)
Documented infection*	16/73 (22)	12/75 (16)
Symptoms		
Temperature, °C	37.7 (0.9)	37.6 (0.8)
Extrathoracic pain, *n* (%)		
Before ACS diagnosis	62 (76)	64 (74)
At ACS diagnosis	6 (7)	13 (15)
Any respiratory symptom, *n*/*N* (%)	79/79 (100)	83/83 (100)
Chest pain, *n*/*N* (%)	74/79 (94)	74/83 (89)
Dyspnea, *n*/*N* (%)	56/79 (71)	60/83 (72)
Cough, *n*/*N* (%)	27/79 (34)	30/83 (36)
Hemoptysis, *n*/*N* (%)	2/79 (3)	1/83 (1)
Any abnormal lung auscultation, *n*/*N* (%)	78/82 (95)	85/86 (99)
Decreased vesicular breath sounds, *n*/*N* (%)	48/79 (62)	47/85 (55)
Tubular breath sounds, *n*/*N* (%)	13/79 (17)	16/85 (19)
Crepitation, *n*/*N* (%)	56/79 (72)	72/85 (85)
Vital signs		
Systolic arterial pressure, mm Hg	125 (113–139)	121 (110–140)
Heart rate, beats/min	101 (19)	101 (17)
Respiratory rate, breaths/min	23 (20–32)	22 (18–29)
Mechanical ventilation		
Noninvasive, *n* (%)	1 (1%)	0
Invasive, *n*	0	0
Blood gases		
Pa_{O_2}, mm Hg	98 (80–123)	93 (73–118)
$F_{I_{O_2}}$, %	27 (22–32)	27 (24–33)
$Pa_{O_2}/F_{I_{O_2}}$ ratio, mm Hg	353 (257–416)	333 (272–405)
$Pa_{O_2}/F_{I_{O_2}} \leq 300$ mm Hg, *n* (%)	29 (35)	34 (40)
Pa_{CO_2}, mm Hg	43 (39–46)	43 (38–46)
Sa_{O_2}, %	97 (95–99)	97 (93–99)
pH	7.4 (7.4–7.4)	7.4 (7.4–7.4)
Lactate, mmol/L	0.7 (0.6–0.9)	0.7 (0.6–1.1)
Laboratory findings		
White cell count, G/L	14.3 (11.52–17.2)	14.6 (11.4–17)
Platelet count, G/L	315 (248–426)	247 (196–396)
Total hemoglobin, g/dL		
All patients	8.4 (1.7)	8.1 (1.5)
SS genotype	8.1 (1.5)	8.0 (1.4)
Lactate dehydrogenase, IU/L	511 (412–682)	636 (430–828)
C-reactive protein, mg/L	92 (62–135)	87 (39–168)
Plasma creatinine, μmol/L	51 (39–59)	53 (45–58)
Creatinine clearance, ml/min	175 (143–221)	160 (143–188)
Prothrombin time, %	71 (13)	71 (11)
Total blood protein concentration, g/L	72 (69–77)	72 (68–77)
CTPA		
Lung parenchymal score on CTPA†	4 (3–6)	4 (3–6)
Management before inclusion		
Patient in ICU before inclusion, *n* (%)	34 (41)	27 (31)
Time from ACS diagnosis to randomization, d	1 (0–2)	1 (1–1)
Time from VOC diagnosis to randomization, d	4 (3–5)	3 (2–4)
Morphine before inclusion, *n*/*N* (%)	66/79 (84)	71/82 (87)
Exchange transfusion before inclusion, *n*/*N* (%)	7/82 (9)	6/83 (7)
Simple transfusion before inclusion, *n*/*N* (%)	5/82 (6)	9/83 (11)
Number of blood units transfused‡	2 (2–2)	2 (2–2)
Simple phlebotomy before inclusion, *n*/*N* (%)	3/82 (4)	0/83 (7)
Volume of blood phlebotomized,§ ml	400 (300–450)	450 (363–575)

Definition of abbreviations: ACS = acute chest syndrome; CTPA = computed tomography with pulmonary angiogram; VOC = vasoocclusive crisis.
*See details in Table E2.
†Each CT scan was divided into four quadrants, defined vertically by the vertebral column and horizontally by the first branch of the left main bronchus. Each quadrant was assigned a score of 0 (normal), 1 (ground-glass opacity), or 2 (consolidation), as previously proposed (23). To calculate the lung parenchymal score (ranging from 0 to 8), the scores of the four quadrants were summed.
‡In transfused patients.
§In patients with phlebotomy.

Table 2. Primary and Secondary Outcomes According to Study Group

	Prophylactic Anticoagulation ($n = 82$)	Therapeutic Anticoagulation ($n = 86$)	Estimate for Between-Group Difference	*P* Value
Primary efficacy outcome				
Time to ACS resolution, Cox model	—	—	HR, 0.71; 95% CI, 0.51 to 0.99	0.04
Supplemental estimates				
Time to ACS resolution, restricted mean ± SE, d	6.1 ± 0.5	4.8 ± 0.4	Δ, −1.33 d; 95% CI, −2.54 to −0.12	0.03
Rate of ACS resolution, *n* (%)	67 (81.7%)	75 (87.2%)	aOR, 1.52; 95% CI, 0.66 to 3.57	0.24
Primary safety outcome				
Major bleeding, *n*	0	0	—	—
Secondary outcomes at hospital discharge				
Nonmajor bleeding, *n*	0	0	—	—
Cumulative dose of parenteral opioids, mg equivalent morphine	219 (65 to 378)	124 (80 to 272)	Δ, −96; 95% CI, −202 to −46	0.02
Mean chest pain score on visual analog scale, cm	1.60 (0.35 to 3.39)	1.07 (0.21 to 2.52)	Δ, −0.50; 95% CI, −1.05 to 0.03	0.06
Exchange transfusion, *n* (%)	15 (18)	10 (12)	OR, 0.57; 95% CI, 0.24 to 1.36	0.2
Simple transfusion, *n* (%)	13 (16)	16 (19)	OR, 1.17; 95% CI, 0.52 to 2.65	0.7
Number of transfused red blood cell packs in transfused patients	2 (2 to 2.3)	2 (2 to 2)	Δ, −0.31; 95% CI, −1.23 to 0.6	0.5
Simple phlebotomy, *n* (%)	2 (2)	1 (1)	OR, 0.47; 95% CI, 0.04 to 5.33	0.5
Volume of phlebotomized blood in patients with phlebotomy, ml	400 (375 to 600)	350 (350 to 825)	Δ, 221; 95% CI, −175 to 618	0.4
High-flow oxygen, *n* (%)	13 (16)	11 (13)	OR, 0.73; 95% CI, 0.30 to 1.77	0.5
Noninvasive mechanical ventilation, *n* (%)	17 (21)	16 (19)	OR, 0.86; 95% CI, 0.40 to 1.84	0.7
Invasive mechanical ventilation, *n* (%)	2 (2.44)	0 (0)	—	>0.99
Catecholamine infusion, *n* (%)	2 (2.44)	0 (0)	—	>0.99
Antibiotics, *n* (%)	71 (87)	76 (88)	OR, 1.16; 95% CI, 0.46 to 2.90	0.8
ICU admission,* *n* (%)	14 (17)	13 (15)	OR, 0.85; 95% CI, 0.37 to 1.95	0.7
Length of ICU stay,* d	4.0 (2.3 to 4.8)	3.5 (2.8 to 5.5)	Δ, −0.07; 95% CI, −3.0 to 2.0	0.96
Hospital death, *n*	0	0	—	—
Time to hospital discharge, restricted mean ± SE, d	8.0 ± 0.7	7.4 ± 0.5	HR, 0.91; 95% CI, 0.67 to 1.25	0.5
Time to hospital discharge, median, d	7.0; 95% CI, 6.0–8.0	6.0; 95% CI, 6.0–7.0		
Any complication†	38 (46%)	37 (43%)	OR, 0.84; 95% CI, 0.45 to 1.56	0.6
Secondary outcomes at 6 mo				
Hospital readmission, *n* (%)	41/79 (52)	43/82 (52)	HR, 1.1; 95% CI, 0.71 to 1.69	0.7
Number of hospital readmissions‡	1 (1 to 2)	1 (1 to 3)	—	0.09
Hospital readmission for ACS, *n*/*N* (%)	12/78 (15)	19/82 (23)	HR, 1.49; 95% CI, 0.72 to 3.1	0.3
Number of hospital readmissions for ACS§	1 (1 to 1)	1 (1 to 1)	—	0.8
Hospital readmission for VOC, *n*/*N* (%)	38/78 (49)	46/82 (56)	HR, 1.28; 95% CI, 0.8 to 1.99	0.3
Deep venous thrombosis, *n*/*N* (%)	1/78 (1.3)	0	—	0.5
Pulmonary artery thrombosis, *n*/*N* (%)	1/78 (1.3)	0	—	0.5

Definition of abbreviations: ACS = acute chest syndrome; aOR = adjusted odds ratio; CI = confidence interval; Δ = difference; HR = hazard ratio; VOC = vasoocclusive crisis.

*Patients admitted to ICU between inclusion and hospital discharge.

†As defined by any of the following: major bleeding, nonmajor bleeding, transfusion, phlebotomy, noninvasive or invasive mechanical ventilation, shock (need for catecholamine infusion), or death.

‡In readmitted patients.

§In patients with hospital readmission for acute chest syndrome.

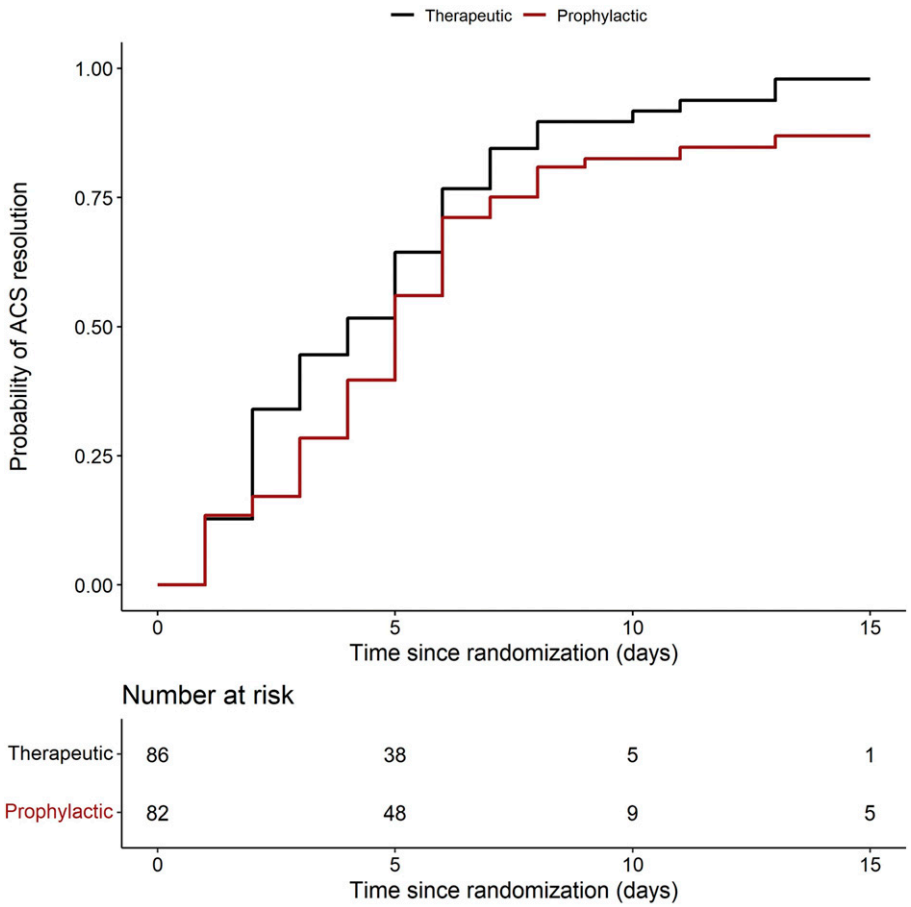

Figure 2. Acute chest syndrome (ACS) resolution. Kaplan-Meier estimated ACS resolution curves for therapeutic and prophylactic anticoagulation groups.

albeit not visible on CT scans, they could play a crucial role in the pathophysiology of the disease and, most interestingly, can be mitigated by a 7-day course of therapeutic anticoagulation. The lack of effect of our intervention on the need for noninvasive or invasive ventilation is likely explained by the fact that the majority of patients were not hypoxemic. However, we cannot exclude the possibility that the benefits of therapeutic anticoagulation might be more pronounced in the peripheral circulation than in the pulmonary circulation.

The vast majority of included patients experienced VOC before or during ACS, a finding in accordance with previous reports (5). In our trial, therapeutic-dose anticoagulation was associated with a significant reduction in morphine consumption compared with prophylactic-dose anticoagulation. These results are consistent with those reported by a prior randomized trial conducted by Qari and colleagues in 253 patients with VOC (39). Qari and colleagues demonstrated a statistically significant reduction in both the number of days with the highest pain scores and the overall duration of the painful crises in participants treated with therapeutic doses of tinzaparin, compared with those who received a placebo. However, the authors could not report on opioid doses. Tinzaparin may exert several favorable effects on endothelial cell activation that accompanies vasoocclusion, including inhibition of endothelial tissue factor pathway (40), tumor necrosis factor-α (40, 41), and von Willebrand factor fibers (42); modulation of nitric oxide (40, 41); and disturbance of P/L-selectin (43) and VLA-4/VCAM-1 (44) interconnections, in addition to its anticoagulant effects. With its lower anti-Xa/anti-IIa ratio, tinzaparin provides a more balanced inhibition of Factor Xa and thrombin than other low-molecular-weight heparins. The direct inhibition of thrombin may contribute to a greater reduction in platelet activation and aggregation (45). This effect could be particularly significant in the context of pulmonary artery thrombosis, where thrombocytosis is a recognized risk factor (38).

Strengths of our study come from the simplicity of the tested treatment; its multicenter, prospective, and double-blind design; the systematic exclusion of pulmonary artery macrothrombosis at randomization; and the selection of a population at low risk of bleeding. Our study has several limitations. First, a relatively small number of patients were randomized, based on assumptions and power calculations for the primary outcome. As such, the study was not specifically powered to detect effect sizes regarding prespecified subgroup analyses, like patients with hypoxemia, leading to potentially limited power. As such, our results could serve as a stimulus for conducting studies involving a greater number of patients with severe disease. In future studies, other patient-centered clinical endpoints could be considered as more robust alternatives to ACS duration. However, TASC is the largest randomized trial ever conducted in patients with ACS regardless of the intervention tested. It was designed to capture the effect of treatment on the speed of ACS resolution, aligning with the intervention's intended mechanism of action. A study designed to alter the likelihood of ACS recovery (which was not our primary aim) would require: *1*) an intervention with the potential to impact recovery rates, which are already very high with standard treatment (>80% at Day 15); and *2*) a substantially larger sample size. Second, the rate of pulmonary artery thrombosis detected on prerandomization CTPA was slightly lower than expected (11) but remains in the range of other reports (38). Third, we included patients in the early phase of ACS (within 48 h of diagnosis); the observed effects may not apply to later stages of the disease. Fourth, we did not include patients attaining the extremes of weight, having renal failure, or having other risk factors for bleeding such as consumptive coagulopathy, which limits the generalizability of the results to all hospitalized ACS cases. However, the good tolerance to therapeutic anticoagulation in our protocol is probably, at least in part, explained by the selection of a population at low risk of bleeding. A similarly good tolerance was previously reported in patients with SCD presenting with VOC (39). Our findings cannot be generalized to children or

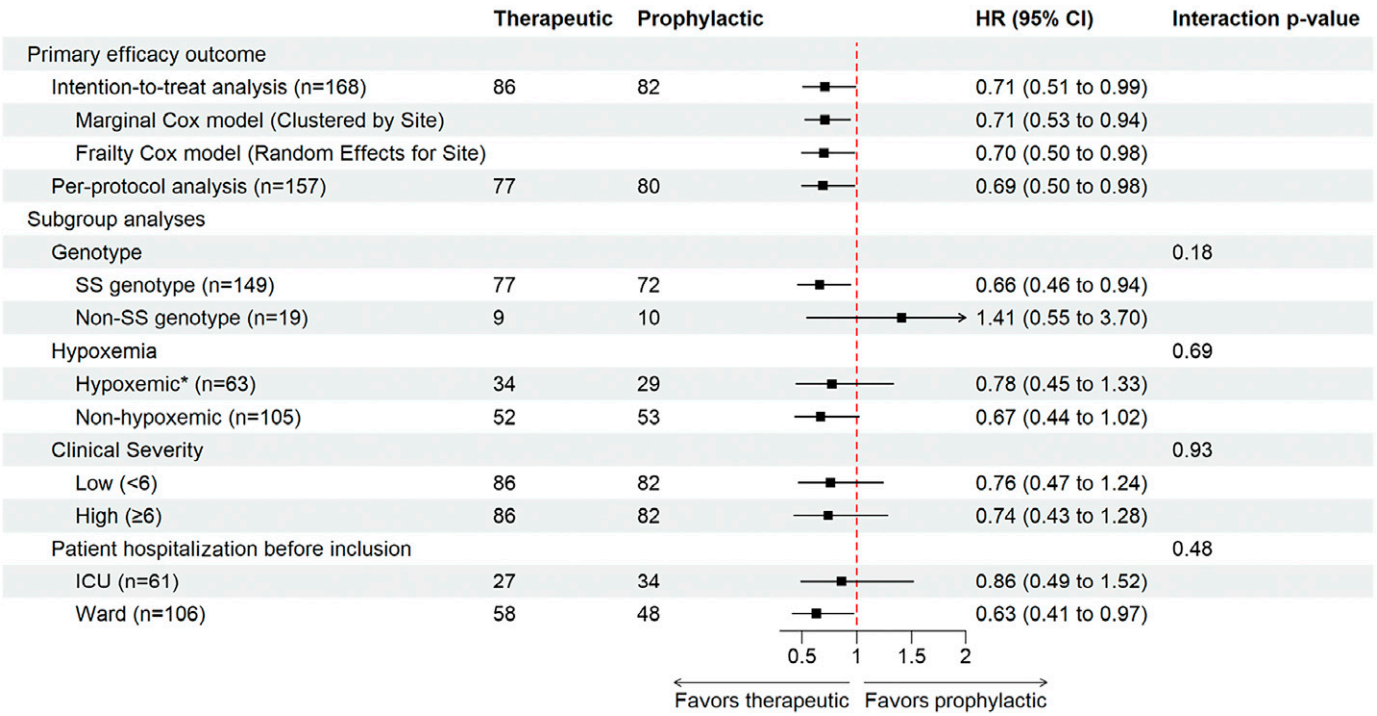

Figure 3. Intention-to-treat, per-protocol, complementary, and subgroup analyses of the primary efficacy outcome (time to acute chest syndrome resolution). CI = confidence interval; HR = hazard ratio. *A ratio of partial pressure of oxygen to fraction of inspired oxygen of <300 mmHg.

adolescents. In this population, the pathophysiology of ACS may differ from that of adults, notably because of the significant role of infections, particularly viral infections, in younger children (7). Furthermore, studies highlighting macrothrombosis in the pulmonary circulation have thus far been limited to the adult population (11). Unlike in France (19), prophylactic anticoagulation is not the standard of care for adults with ACS in some countries. Therefore, testing a third group without anticoagulation could be justified. Fifth, we did not quantify microvascular thrombosis on CTPA because there was no routine evaluation of the microvascular beds on CT scans or scintigraphy in the trial centers.

Conclusions

In the TASC trial, therapeutic-dose anticoagulation improved the primary efficacy outcome (i.e., time to ACS resolution), without increasing the bleeding risk, compared with prophylactic-dose anticoagulation, in adult patients with ACS and no initial pulmonary artery macrothrombosis. Results were consistent in the subgroup of patients with the SS genotype. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank all those who worked/participated to make the TASC trial successful, including the patients enrolled in this trial, all site staff who helped to enroll participants, and all healthcare professionals who took care of our patients throughout this protocol duration. In particular, the authors thank Pr. Elie Azoulay, M.D., Ph.D. (Intensive Care Unit, Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris, Paris, France), Dr. Candice Estellat, M.D. (Clinical Research Unit, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Paris, France), and Dr. Françoise Driss, M.D. (Internal Medicine and Immunology, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, France) for joining the Data and Safety Monitoring Board. They also thank S. Baloul, S. Hadibi, I Haraket, K. Bouaziz, T. Sadaoui, F. Ouali, and L. Nait Chabane (Clinical Research Unit, Hôpitaux universitaires Henri-Mondor, Assistance Publique-Hôpitaux de Paris, Créteil, France) for their help with data collection.

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