ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

ABSTRACT

BACKGROUND

Thrombosis and inflammation may contribute to the risk of death and complications among patients with coronavirus disease 2019 (Covid-19). We hypothesized that therapeutic-dose anticoagulation may improve outcomes in noncritically ill patients who are hospitalized with Covid-19.

METHODS

In this open-label, adaptive, multiplatform, controlled trial, we randomly assigned patients who were hospitalized with Covid-19 and who were not critically ill (which was defined as an absence of critical care–level organ support at enrollment) to receive pragmatically defined regimens of either therapeutic-dose anticoagulation with heparin or usual-care pharmacologic thromboprophylaxis. The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death (assigned a value of –1) and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge. This outcome was evaluated with the use of a Bayesian statistical model for all patients and according to the baseline D-dimer level.

RESULTS

The trial was stopped when prespecified criteria for the superiority of therapeutic-dose anticoagulation were met. Among 2219 patients in the final analysis, the probability that therapeutic-dose anticoagulation increased organ support–free days as compared with usual-care thromboprophylaxis was 98.6% (adjusted odds ratio, 1.27; 95% credible interval, 1.03 to 1.58). The adjusted absolute between-group difference in survival until hospital discharge without organ support favoring therapeutic-dose anticoagulation was 4.0 percentage points (95% credible interval, 0.5 to 7.2). The final probability of the superiority of therapeutic-dose anticoagulation over usual-care thromboprophylaxis was 97.3% in the high D-dimer cohort, 92.9% in the low D-dimer cohort, and 97.3% in the unknown D-dimer cohort. Major bleeding occurred in 1.9% of the patients receiving therapeutic-dose anticoagulation and in 0.9% of those receiving thromboprophylaxis.

CONCLUSIONS

In noncritically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis. (ATTACC, ACTIV-4a, and REMAP-CAP ClinicalTrials.gov numbers, NCT04372589, NCT04505774, NCT02735707, and NCT04359277.)

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This article was published on August 4, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2105911

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In some patients, the clinical course of coronavirus disease 2019 (Covid-19) is characterized by an initial period of mild-to-moderate symptoms, followed by progressive respiratory failure leading to cardiovascular or respiratory organ support or death.[1,2] However, the majority of patients who are hospitalized with Covid-19 are moderately ill and do not initially require organ support in an intensive care unit (ICU).[3-5] Limited therapies are available to prevent progression to organ failure and death among moderately ill patients.

Patients who are hospitalized with Covid-19 frequently have macrovascular and microvascular thrombosis and inflammation, which are associated with a poor clinical outcome.[6,7] Given the antithrombotic, antiinflammatory, and possibly antiviral properties of heparins,[8-10] it has been hypothesized that anticoagulation with heparin administered at doses higher than conventionally used for venous thromboprophylaxis may improve outcomes.[11] Furthermore, an elevated D-dimer level has been associated with vascular thrombosis and a poor clinical outcome.[6,12] Thus, some practitioners have advocated an evaluation of D-dimer levels to guide anticoagulant administration. In the absence of data from randomized trials, clinical-guideline recommendations[13] and practice[14] vary widely.

We conducted an international, adaptive, multiplatform, randomized, controlled trial to determine whether an initial strategy of therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin improves in-hospital survival and reduces the duration of ICU-level cardiovascular or respiratory organ support among hospitalized patients with Covid-19 who are not critically ill.

Methods

Trial Design and Oversight

To accelerate evidence generation, we integrated three platforms evaluating therapeutic-dose anticoagulation with heparin in patients hospitalized with Covid-19 into a single multiplatform, randomized, controlled trial. The participating platforms were Antithrombotic Therapy to Ameliorate Complications of Covid-19 (ATTACC),[15] A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19 (ACTIV-4a), and Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP).[16] During the trial period, patients with moderate Covid-19 disease were enrolled at 121 sites in 9 countries (the United States, Canada, the United Kingdom, Brazil, Mexico, Nepal, Australia, the Netherlands, and Spain). We prospectively aligned eligibility criteria, interventions, outcome measures, and data collection. (Comparisons of the three platforms are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Independent data and safety monitoring boards oversaw the platforms on the basis of a collaborative cross-platform interaction plan. The trial protocols and unified statistical analysis plan are also available at NEJM.org.

The trial was approved by the relevant ethics committees and conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation. All the patients or their surrogates provided written or oral informed consent, in accordance with regional regulations. The trial was supported by multiple international funding organizations, which had no role in the design, analysis, or reporting of trial results, apart from the ACTIV-4a protocol, which received input on design from professional staff members at the National Institutes of Health and from peer reviewers. The members of the writing committees vouch for the accuracy and completeness of the data and for the fidelity of the trials to the protocols.

Patients

The multiplatform trial enrolled patients who were hospitalized with Covid-19. The investigators hypothesized that the benefits and risks of therapeutic-dose anticoagulation would vary according to disease severity. As such, the design prospectively stratified patients according to whether they had severe disease (ICU-level care or critically ill) or moderate disease (hospitalized but noncritically ill) at enrollment. This report describes the results of the analyses involving patients with moderate Covid-19; the results of analyses involving patients with severe Covid-19 are reported separately.[17]

Moderate disease severity was defined as hospitalization for Covid-19 without the need for ICU-level care. ICU-level care was defined as the use of respiratory or cardiovascular organ support

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(oxygen delivered by high-flow nasal cannula, noninvasive or invasive mechanical ventilation, or the use of vasopressors or inotropes) in an ICU. In ACTIV-4a, in which investigators found that ICU-level care was challenging to define during the pandemic, receipt of organ support, regardless of hospital setting, was used to define ICU-level care. Patients who were admitted to an ICU but without receiving qualifying organ support were considered to be moderately ill.

Patients with moderate disease were further stratified according to their baseline D-dimer level as follows: a high D-dimer level (≥2 times the upper limit of the normal range [ULN], according to local laboratory criteria), a low D-dimer level (<2 times the ULN), and an unknown D-dimer level. Patients were ineligible for enrollment in the ATTACC and ACTIV-4a platforms if 72 hours had elapsed since hospital admission for Covid-19 or since in-hospital confirmation of the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); in the REMAP-CAP platform, patients were ineligible if 14 days had elapsed since admission. Patients were also excluded if hospital discharge was expected within 72 hours or if they had a clinical indication for therapeutic anticoagulation, a high risk of bleeding, receipt of dual antiplatelet therapy, or a known heparin allergy, including heparin-induced thrombocytopenia (HIT). (Details regarding eligibility are provided in the Supplementary Appendix.)

RANDOMIZATION

We used central Internet-based systems to randomly assign patients to receive either therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin or usual-care pharmacologic thromboprophylaxis in an open-label fashion. Therapeutic-dose anticoagulation was administered according to local protocols for the treatment of acute venous thromboembolism for up to 14 days or until recovery; the latter was defined as hospital discharge or a discontinuation of supplemental oxygen for at least 24 hours. Thromboprophylaxis was provided at a dose and duration determined by the treating clinician according to local practice. The anticoagulation and thromboprophylaxis regimens are detailed in the Supplementary Appendix.

Treatments were initially randomly assigned in a 1:1 ratio. The ATTACC and REMAP-CAP designs specified the possibility of response-adaptive randomization, in which group-assignment ratios could be modified in a blinded fashion during the trial on the basis of response-adaptive interim analyses to favor the assignment of patients to the treatment group showing greater benefit. (Details regarding the methods used in adaptive randomization are provided in the Supplementary Appendix.) A subset of patients in the REMAP-CAP platform underwent randomization to other platform domains, including an antiplatelet domain.

OUTCOME MEASURES

The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge. Patients who were discharged from the hospital before day 21 were assumed to be alive and free of organ support through day 21. Any death during the index hospitalization through 90 days was assigned the worst score on the outcome scale (–1). This end point reflects both the use of ICU-level interventions and survival, with higher values indicating better outcomes.

Secondary efficacy outcomes included survival until hospital discharge, survival without receipt of organ support, survival without receipt of invasive mechanical ventilation, survival without mechanical respiratory support, length of hospital stay, a major thrombotic event or death (a composite of myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, or in-hospital death), and any thrombotic event including deep venous thrombosis. Secondary safety outcomes that were assessed during the treatment period were major bleeding (as defined according to the criteria of the International Society on Thrombosis and Haemostasis[18]) and laboratory-confirmed HIT. All reported bleeding and thrombotic events were adjudicated in a blinded fashion by clinical end-points committees using consensus definitions (as described in the Supplementary Appendix).

STATISTICAL ANALYSIS

We performed the primary analysis using a Bayesian cumulative logistic model that calculated the posterior probability distribution for the proportional odds ratio for therapeutic-dose anticoagulation as compared with usual-care thrombopro-

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phylaxis with respect to organ support–free days in patients with confirmed SARS-CoV-2 infection. Although REMAP-CAP enrolled patients with suspected or confirmed Covid-19, only patients who had infection that was confirmed by laboratory testing were included in the main analyses. The primary model incorporated weakly informative Dirichlet prior distributions for the number of days without organ support and was adjusted for age, sex, trial site, D-dimer cohort, and enrollment period (in 2-week intervals). The model was fitted with the use of a Markov chain Monte Carlo algorithm with 100,000 samples from the joint posterior distribution, which allowed for calculation of the posterior distributions for the proportional odds ratios, including medians and 95% credible intervals, and the posterior probabilities of superiority and futility for the comparison between therapeutic-dose anticoagulation and usual-care thromboprophylaxis.

The primary model estimated treatment effects for each of the groups according to disease severity (severe or moderate, with the latter stratified according to the baseline D-dimer level) by means of a Bayesian hierarchical method. The treatment effects of anticoagulation for the groups were nested in a hierarchical prior distribution centered on an overall intervention effect estimated with a neutral prior distribution, but distinct group-specific effects were estimated. With regard to the primary outcome of organ support–free days, when consistent effects were observed for the groups, the posterior distribution for each intervention group effect was shrunk toward the overall estimate (dynamic borrowing).[19] Secondary end points were modeled without dynamic borrowing. The stopping criteria for treatment superiority (>99% probability of an odds ratio of >1.0) and futility (<5% probability of an odds ratio of >1.2) were evaluated monthly by an independent statistical analysis committee and could be reached separately in the low and high D-dimer subgroups at each adaptive analysis; no stopping criteria were defined for the cohort with an unknown D-dimer level. Several sensitivity analyses of the primary model are also reported. (Details regarding the sensitivity analyses are provided in the Supplementary Appendix.) In addition, we present analyses involving patients with moderate disease that assume a single treatment effect regardless of the D-dimer level.

Subgroup analyses assessed the treatment effect according to age, sex, baseline respiratory support, and dose of thromboprophylactic drugs. Protocol adherence was defined according to the anticoagulant dose equivalent administered within the first 24 to 48 hours after randomization. The receipt of doses that were categorized as therapeutic or subtherapeutic heparin qualified as adherence in the therapeutic-dose anticoagulation group, and the receipt of low-dose or intermediate-dose thromboprophylactic drugs qualified as adherence in the usual-care thromboprophylaxis group.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The first patients underwent randomization on April 21, 2020. On January 22, 2021, enrollment was discontinued on the advice of the data and safety monitoring boards after a planned adaptive analysis of data from 1398 patients showed that the prespecified stopping criteria for superiority of therapeutic-dose anticoagulation had been reached in both the high and low D-dimer cohorts (Table S1 in the Supplementary Appendix). By that time, 2244 patients with moderate disease had undergone randomization. The primary analysis population consisted of 2219 patients (Fig. 1). Parallel enrollment of patients with severe Covid-19 ran through December 19, 2020, as reported separately.[17]

Baseline characteristics were similar in the two treatment groups (Table 1), including within each D-dimer cohort (Table S2). Patients in the high and unknown D-dimer cohorts were generally older and had a higher prevalence of coexisting illnesses than those in low D-dimer cohort. Concomitant baseline therapies included antiplatelet agents (in 12% of the patients), glucocorticoids (in 62%), and remdesivir (in 36%).

Initial adherence to the protocol-assigned anticoagulation dose after randomization was 88.3% in the therapeutic-dose anticoagulation group and 98.3% in the thromboprophylaxis group (Table S3). Of the 1093 patients in the therapeutic-dose anticoagulation group with available data, 1035 (94.7%) received a low-molecular-weight heparin, most commonly enoxaparin. Among the 855 patients in the thromboprophylaxis group with available data, 613 (71.7%) received a low dose of a thromboprophylactic drug and 227 (26.5%) received an intermediate dose.

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PRIMARY OUTCOME

Among 2219 participants with moderate disease, the posterior probability that therapeutic-dose anticoagulation increased organ support–free days as compared with usual-care thromboprophylaxis was 98.6% (median adjusted odds ratio, 1.27; 95% credible interval, 1.03 to 1.58) (Table 2). Of the 1048 patients in the usual-care thromboprophylaxis group, 801 (76.4%) survived until hospital discharge without receipt of organ support

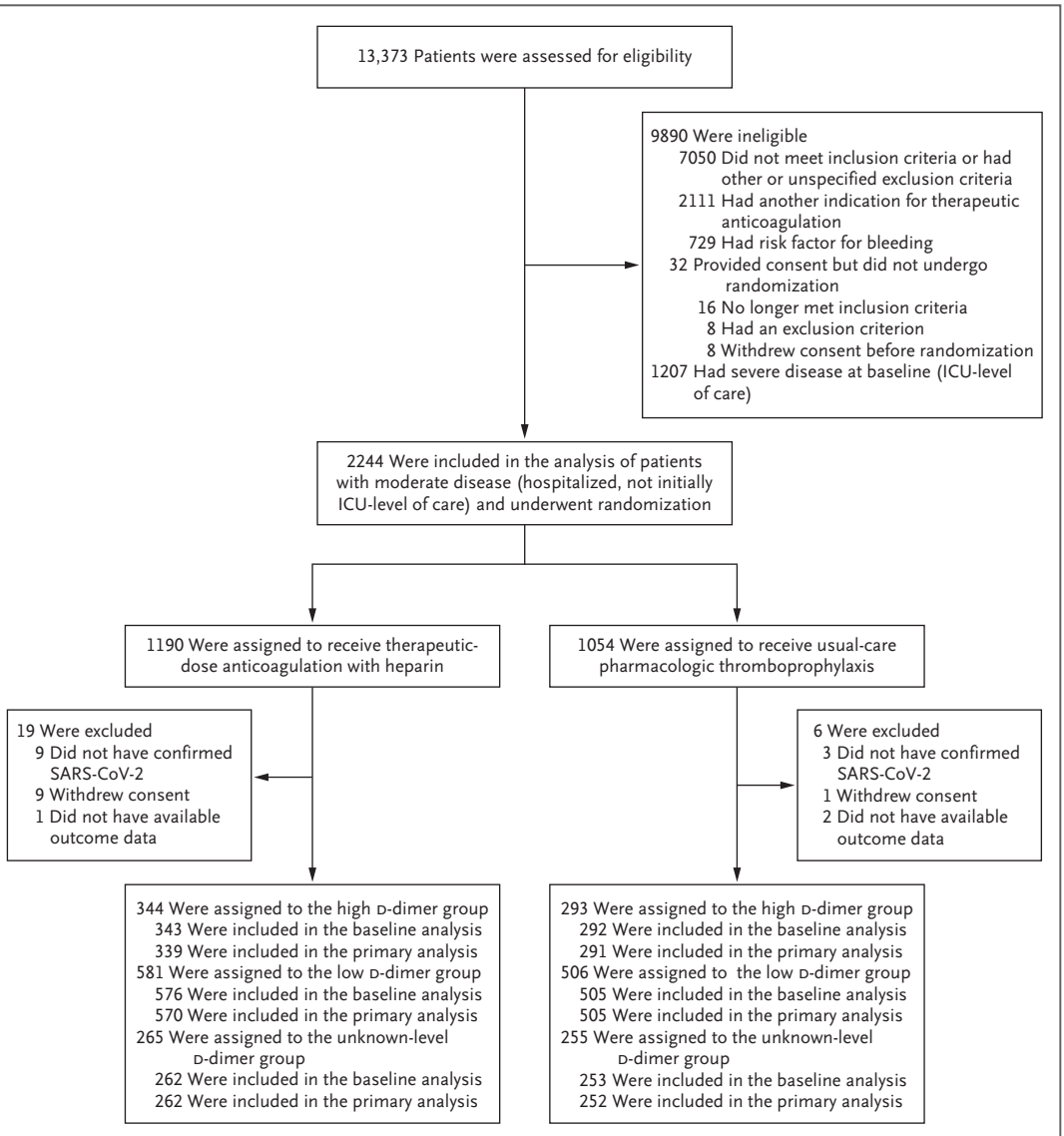


Figure 1. Screening, Enrollment, and Randomization, According to Trial Group.

Trial sites used varying screening and documentation practices during the coronavirus disease 2019 (Covid-19) pandemic to identify eligible patients, as described in the protocol. Of the 13,373 patients who underwent screening, 7202 were assessed for eligibility in the ATTACC platform, 3799 in the ACTIV-4a platform, and 2372 in the REMAP-CAP platform. Under reasons for exclusion from the trial, "other" includes not meeting an inclusion criterion (including a lack of diagnosis of Covid-19), an anticipated duration of hospital stay of less than 72 hours, or meeting an exclusion criterion that is not specified here. Data for patients who had severe disease at baseline could be used for covariate adjustment and dynamic borrowing calculations in the primary analysis. The numbers of patients who were randomly assigned to the treatment groups were imbalanced owing to the use of response-adaptive randomization.

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Therapeutic-Dose Anticoagulation (N = 1181)	Usual-Care Thromboprophylaxis (N = 1050)
Age ±SD — yr	59.0±14.1	58.8±13.9
Male sex — no. (%)	713 (60.4)	597 (56.9)
Race or ethnic group — no./total no. (%)†		
White	622/994 (62.6)	564/845 (66.7)
Asian	41/994 (4.1)	43/845 (5.1)
Black	219/994 (22.0)	162/845 (19.2)
First Nations or American Indian	118/965 (12.2)	82/819 (10.0)
Other	17/1109 (1.5)	16/968 (1.7)
Hispanic or Latino	574/1004 (57.2)	537/879 (61.1)
Median body-mass index (IQR)‡	29.8 (26.3–34.7)	30.3 (26.7–34.9)
Preexisting condition — no./total no. (%)		
Hypertension	546/1023 (53.4)	447/892 (50.1)
Diabetes mellitus	352/1181 (29.8)	311/1049 (29.6)
Severe cardiovascular disease§	123/1165 (10.6)	121/1038 (11.7)
Chronic kidney disease	83/1173 (7.1)	69/1037 (6.7)
Chronic respiratory disease¶	249/1132 (22.0)	212/988 (21.5)
Immunosuppressive disease	105/1143 (9.2)	103/1005 (10.2)
Treatment — no./total no. (%)		
Antiplatelet agent‖	148/1140 (13.0)	111/1013 (11.0)
Remdesivir	428/1178 (36.3)	383/1048 (36.5)
Glucocorticoid	479/791 (60.6)	415/656 (63.3)
Tocilizumab	6/1178 (0.5)	7/1048 (0.7)
Respiratory support — no. (%)		
None	156 (13.2)	123 (11.7)
Low-flow nasal cannula or face mask	789 (66.8)	696 (66.3)
High-flow nasal cannula	25 (2.1)	28 (2.7)
Noninvasive mechanical ventilation	21 (1.8)	24 (2.3)
Unspecified**	190 (16.1)	179 (17.0)
Median laboratory value (IQR)		
Median D-dimer level relative to ULN at trial site	1.6 (0.9–2.6)	1.5 (1.0–2.7)
Platelets — per mm^3	221,000 (171,000–290,000)	218,000 (172,500–289,000)
Lymphocytes — per mm^3	900 (700–1300)	1000 (700–1400)
Creatinine — mg/dl	0.9 (0.7–1.1)	0.9 (0.7–1.1)
Platform of enrollment — no. (%)††		
ATTACC‡‡	650 (55.0)	509 (48.5)
ACTIV-4a	387 (32.8)	392 (37.3)
REMAP-CAP	144 (12.2)	149 (14.2)
Country of enrollment — no./total no. (%)		
United Kingdom	95/1181 (8.0)	103/1050 (9.8)
United States	573/1181 (48.5)	507/1050 (48.3)

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Table 1. (Continued)

Characteristic	Therapeutic-Dose Anticoagulation (N=1181)	Usual-Care Thromboprophylaxis (N=1050)
Canada	102/1181 (8.6)	83/1050 (7.9)
Brazil	234/1181 (19.8)	209/1050 (19.9)
Other§§	177/1181 (15.0)	148/1050 (14.1)

* Listed are data that were included in the analysis involving patients with moderate severity of coronavirus disease 2019 (Covid-19). The denominators of patients in the anticoagulation group and the thrombophylaxis group are unequal owing to response-adaptive randomization. The baseline characteristics of the patients according to D-dimer level are provided in Table S2 in the Supplementary Appendix. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ULN denotes upper limit of the normal range.
† Race or ethnic group was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Severe cardiovascular disease was defined as a baseline history of heart failure, myocardial infarction, coronary artery disease, peripheral arterial disease, or cerebrovascular disease (stroke or transient ischemic attack) in the ATTACC (Antithrombotic Therapy to Ameliorate Complications of Covid-19) and ACTIV-4a (A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19) platforms and as a baseline history of New York Heart Association class IV symptoms in the REMAP-CAP platform (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia).
¶ Chronic respiratory disease was defined as a baseline history of asthma, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, primary lung cancer, pulmonary hypertension, active tuberculosis, or the receipt of home oxygen therapy.
‖ Not listed are 74 patients who were coenrolled in the REMAP-CAP Antiplatelet Domain (39 in the anticoagulation group and 35 in the thromboprophylaxis group).
** In REMAP-CAP, levels of oxygen support (including no support) below the level of high-flow nasal cannula were not reported.
†† The relative proportion of patients who were randomly assigned in each platform was imbalanced owing to implementation of response-adaptive randomization in ATTACC on December 15, 2020.
‡‡ A total of 215 patients who were enrolled in the ATTACC platform were funded by the ACTIV4a platform by the National Heart, Lung, and Blood Institute.
§§ Other participating countries were Mexico, Nepal, Australia, the Netherlands, and Spain.

during the first 21 days, as compared with 939 of 1171 patients (80.2%) in the therapeutic-dose anticoagulation group. The median adjusted absolute difference in this value was 4.0 percentage points (95% credible interval, 0.5 to 7.2), favoring the anticoagulation group. Because the majority of patients in the two treatment groups survived until hospital discharge without receipt of ICU-level organ support, the median value for organ support–free days was 22 in both groups (Fig. 2 and Fig. S1). Accordingly, the proportion of patients in each treatment group who survived until hospital discharge without receipt of organ support (22 on the ordinal scale) is reported.

In the primary adaptive analysis groups, the final posterior probability for superiority of therapeutic-dose anticoagulation as compared with usual-care thromboprophylaxis was 97.3% in the high D-dimer cohort, 92.9% in the low D-dimer cohort, and 97.3% in the cohort with an unknown D-dimer level (Table 2 and Fig. S1). The results were consistent in sensitivity analyses (Tables S4 and S5).

Among all the patients with moderate disease, the treatment effect did not vary meaningfully according to age, level of respiratory support at enrollment, or dose of thromboprophylactic drugs. There was a 95.2% probability that the odds ratio associated with therapeutic-dose anticoagulation was higher in men than in women (Fig. S2).

SECONDARY OUTCOMES

Secondary outcomes are shown in Table 3, Table S6, and Figure S3. In the overall cohort of patients with moderate disease, the posterior probability that therapeutic-dose anticoagulation increased survival until hospital discharge as compared with thromboprophylaxis was 87.1% (median adjusted odds ratio, 1.21; 95% credible interval, 0.87 to 1.68), for a median adjusted between-group difference of 1.3 percentage points (95% credible interval, –1.1 to 3.2). The posterior probabilities that patients in the therapeutic-dose anticoagulation group were more likely to survive without organ support or sur-

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Table 2. Primary Outcome of Organ Support–Free Days.*

Variable	Therapeutic-Dose Anticoagulation	Usual-Care Thromboprophylaxis	Adjusted Difference in Risk (95% Credible Interval)†	Adjusted Odds Ratio (95% Credible Interval)‡	Probability of Superiority of Therapeutic-Dose Anticoagulation
	no. of patients/total no. (%)		*percentage points*		%
Patients with moderate disease					
Overall group§	939/1171 (80.2)	801/1048 (76.4)	4.0 (0.5 to 7.2)	1.27 (1.03–1.58)	98.6
D-dimer cohort¶					
High level	264/339 (77.9)	210/291 (72.2)	5.1 (0.0 to 9.9)	1.31 (1.00–1.76)	97.3
Low level	463/570 (81.2)	403/505 (79.8)	3.0 (–1.2 to 6.3)	1.22 (0.93–1.57)	92.9
Unknown level	212/262 (80.9)	188/252 (74.6)	4.9 (0.00 to 9.9)	1.32 (1.00–1.86)	97.3

* The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge. Because the majority of patients in the two treatment groups survived until hospital discharge without receipt of critical care–level organ support, the median value for organ support–free days was 22 in both groups. Accordingly, the proportion of patients in each treatment group who survived until hospital discharge without receipt of organ support (22 on the ordinal scale) is reported.

† The adjusted difference in risk is based on the event frequency in the usual-care thromboprophylaxis group and the odds ratio after adjustment for age, sex, site, D-dimer group, and enrollment period.

‡ The odds ratio is for the therapeutic-dose anticoagulation group as compared with the usual-care thromboprophylaxis group. The odds ratios are adjusted for age, sex, trial site, D-dimer cohort, and enrollment period, which may be imbalanced due to the use of response-adaptive randomization.

§ This model assumes a single treatment effect in all the patients with moderate disease regardless of the baseline D-dimer level. Dynamic borrowing of information on the treatment effect from patients who had severe illness at baseline was permitted, in which similar treatment effects were grouped together on the basis of their degree of similarity. Results from a sensitivity analysis assuming independent treatment effects between disease-severity cohorts are provided in Table S5 in the Supplementary Appendix.

¶ The primary adaptive model estimated treatment effects with the use of a Bayesian hierarchical approach in the following groups: patients with severe disease and those with moderate disease stratified according to their baseline high D-dimer level (≥2 times the ULN, low D-dimer level (<2 times the ULN), or unknown D-dimer level. This model permitted dynamic borrowing across illness-severity and D-dimer cohorts, in which similar treatment effects are grouped together on the basis of their degree of similarity. Accordingly, observations about treatment effect are shared between groups. Results from a sensitivity analysis assuming independent treatment effects among D-dimer–defined cohorts are also provided in Table S5.

vive without invasive mechanical ventilation at 28 days were 99.1% and 92.2%, respectively.

A major thrombotic event or in-hospital death occurred in 94 of 1180 patients (8.0%) in the therapeutic-dose anticoagulation group and in 104 of 1046 patients (9.9%) in the thromboprophylaxis group (Table 3 and Tables S6 and S7). The analysis of the end point incorporating the occurrence of deep venous thrombosis had similar results. Major bleeding occurred in 22 of 1180 patients (1.9%) in the therapeutic-dose anticoagulation group and in 9 of 1047 (0.9%) in the usual-care thromboprophylaxis group (Table S8). Fatal bleeding occurred in 3 patients in the anticoagulation group and in 1 patient in the thromboprophylaxis group. There were no episodes of intracranial bleeding or confirmed HIT.

DISCUSSION

In noncritically ill patients hospitalized with Covid-19, therapeutic-dose anticoagulation with heparin (most commonly, low-molecular-weight heparin) increased the probability of survival until hospital discharge with a reduced need for ICU-level organ support at 21 days as compared with usual-care thromboprophylaxis. Therapeutic-dose anticoagulation was beneficial regardless of the patient's baseline D-dimer level. Major bleeding occurred more frequently in the anticoagulation group (1.9% vs. 0.9%). On the basis of these findings, for every 1000 hospitalized patients with moderate disease, an initial strategy of therapeutic-dose anticoagulation, as compared with usual-care thromboprophylaxis, would be anticipated to result in the survival of 40 additional patients until hospital discharge without organ support at the expense of 7 additional major bleeding events. Absolute treatment benefits were more apparent in the high D-dimer cohort than in the low D-dimer cohort. Patients in the high D-dimer cohort were generally older and had a higher prevalence of coexisting illnesses than those in the low D-dimer cohort.

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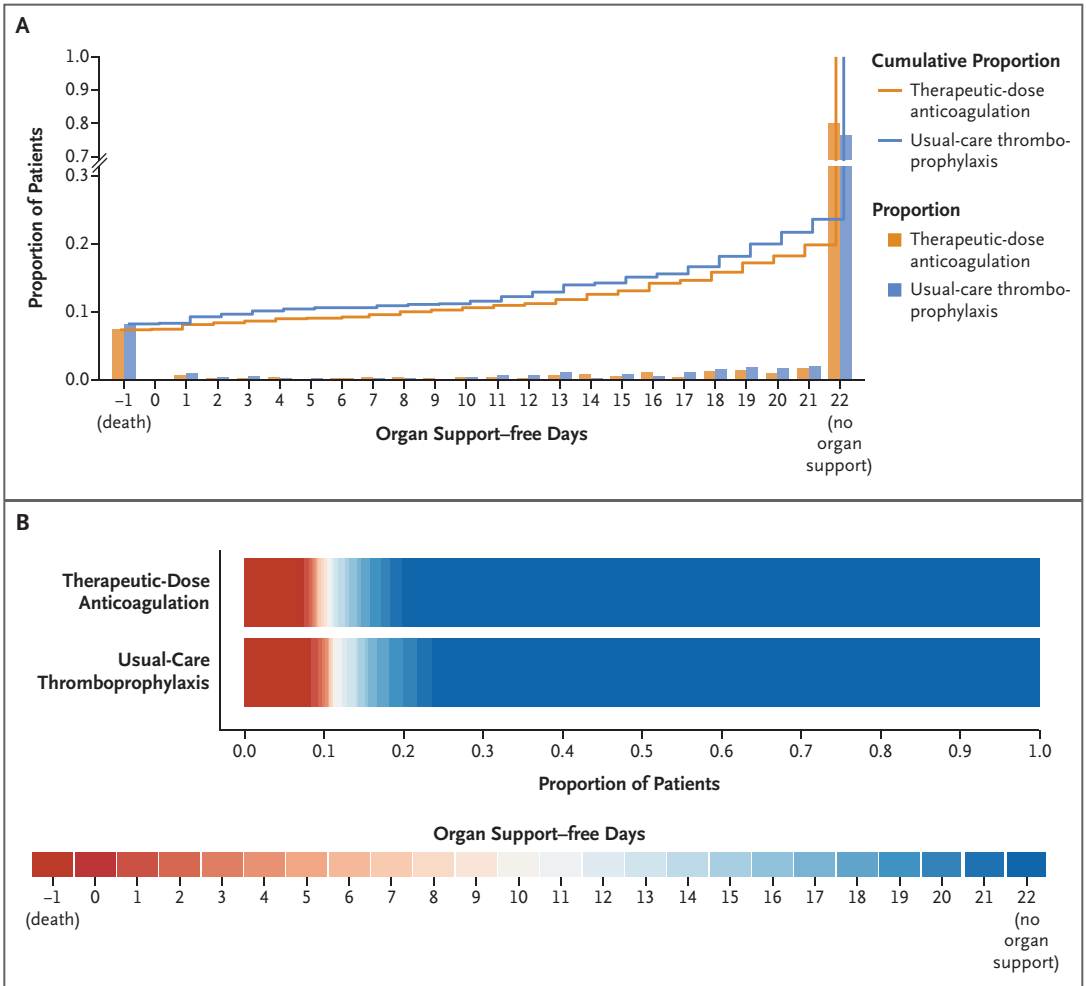


Figure 2. Days without Organ Support among All the Patients with Moderate Disease.

Panel A shows the distribution of organ support–free days among all the patients with moderate disease. The ordinal scale includes a score of –1 (in-hospital death, the worst possible outcome), a score of 0 to 21 (the numbers of days alive without organ support), and a score of 22 (survival until hospital discharge without receipt of organ support, the best possible outcome). The difference in the height of the two curves at any point represents the difference in the cumulative probability of having a value for days without organ support of less than or equal to that point on the x axis. Panel B shows the number of days without organ support as horizontally stacked proportions of patients in the two treatment groups, with the following possible outcomes: in-hospital death with or without the receipt of organ support (dark red, the worst possible outcome, corresponding to a score of –1 on the ordinal scale); survival with organ support provided in an intensive care unit (ICU) (red-to-blue gradient shading based on the number of days alive without organ support; intermediate outcome, corresponding to a score of 0 to 21 on the ordinal scale); and survival until hospital discharge without ICU-level organ support (dark blue, the best possible outcome, corresponding to a score of 22 on the ordinal scale).

Several cohort studies have shown a favorable association between anticoagulant use and survival from Covid-19.[20-22] Because SARS-CoV-2 infection incites a dysregulated inflammatory response that may lead to activation of coagulation[23] and potentially contribute to organ failure,[24-26] heparins may reduce the use of organ support through antithrombotic, antiinflammatory, and potentially antiviral mechanisms.[8-10,27]

In contrast to the benefit we found in noncritically ill patients, a parallel analysis from the same multiplatform trial showed that empirical therapeutic-dose anticoagulation was not beneficial in critically ill patients (i.e., those receiving

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Table 3. Secondary Outcomes among All Patients with Moderate Disease.*

Outcome	Therapeutic-Dose Anticoagulation	Usual-Care Thromboprophylaxis	Adjusted Difference in Risk (95% Credible Interval)†	Adjusted Odds Ratio (95% Credible Interval)‡	Probability of Effect of Therapeutic-Dose Anticoagulation
	no. of patients/total no. (%)		*percentage points*		%
Survival until hospital discharge	1085/1171 (92.7)	962/1048 (91.8)	1.3 (–1.1 to 3.2)	1.21 (0.87 to 1.68)§	87.1¶
Survival without organ support at 28 days‖	932/1175 (79.3)	789/1046 (75.4)	4.5 (0.9 to 7.7)	1.30 (1.05 to 1.61)	99.1¶
Progression to intubation or death**	129/1181 (10.9)	127/1050 (12.1)	–1.9 (–4.1 to 0.7)	0.82 (0.63 to 1.07)	92.2¶
Major thrombotic event or death	94/1180 (8.0)	104/1046 (9.9)	–2.6 (–4.4 to –0.2)	0.72 (0.53 to 0.98)	98.0¶
Major thrombotic event	13/1180 (1.1)	22/1046 (2.1)			
Death in hospital	86/1180 (7.3)	86/1046 (8.2)			
Major bleeding	22/1180 (1.9)	9/1047 (0.9)	0.7 (–0.1 to 2.3)	1.80 (0.90 to 3.74)	95.5††

* Secondary end points were modeled without dynamic borrowing. In these analyses, a single treatment effect was assumed regardless of the D-dimer level. Additional secondary end points, including those categorized according to the D-dimer cohort, are provided in Table S6.
† The adjusted difference in risk is based on the event rate in the usual-care thromboprophylaxis group and the odds ratio after adjustment for age, sex, site, D-dimer cohort, and enrollment period.
‡ The odds ratio is for the therapeutic-dose anticoagulation group as compared with the usual-care thromboprophylaxis group. The odds ratios are adjusted for age, sex, trial site, D-dimer cohort, and enrollment period, which may be imbalanced due to the use of response-adaptive randomization.
§ In a model that included borrowing of information on treatment effect from patients with severe disease, the median adjusted odds ratio for survival until hospital discharge was 1.18 (95% credible interval, 0.86 to 1.63), with a posterior probability of superiority of 84.4%.
¶ In this category, the probability of superiority is shown.
‖ Survival without organ support at 28 days was modeled as a dichotomous outcome. Similar results were obtained after the exclusion of 52 patients who were receiving organ support at baseline (median adjusted odds ratio, 1.30; 95% credible interval, 1.06 to 1.62), with a posterior probability of superiority of 99.3%.
** Progression to intubation or death was modeled as an ordinal outcome with death as the worst possible outcome.
†† For major bleeding, the probability of inferiority is shown.

ICU-level care at enrollment).[19] In a separate randomized trial involving critically ill patients with Covid-19, intermediate-dose heparin was likewise not beneficial.[28] It is possible that therapeutic-dose heparin cannot influence the cascade of inflammation, thrombosis, and organ injury in patients with advanced disease.[29-31] It is also possible that differences in the patient populations, aside from illness severity, may have contributed to these findings.

In our multiplatform trial, we used an adaptive Bayesian design that allowed for trial conclusions to be reached simultaneously or sequentially in groups defined according to illness severity and D-dimer level through periodic adaptive analyses. A statistical method of dynamic borrowing was incorporated to enable the investigators to reach conclusions more quickly across the D-dimer stopping cohorts in which the estimates of treatment effect were similar and to mitigate the influence of outlying treatment effects by shrinking similar treatment estimates together. Response-adaptive randomization allowed blinded randomization probabilities to be modified as evidence about treatment effects was accrued throughout the trial. Since response-adaptive randomization may lead to imbalances in baseline covariates between treatment groups over time, the primary models were necessarily adjusted for age, sex, trial site, D-dimer cohort, and enrollment period. Therefore, absolute between-group differences in risk that are based on adjusted treatment effects and the observed frequencies of control events are presented. The adjusted absolute between-group difference in outcomes that is presented is a median, so patients at higher baseline risk may derive greater absolute benefit.

The open-label design of the trial represents a potential limitation, although the primary outcome involving survival and receipt of organ support was selected to minimize bias and to function across a spectrum of illness severity.

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The potential for ascertainment bias cannot be excluded for the secondary outcomes of major bleeding or thrombosis. This factor, along with the absence of protocol-specified screening for venous thrombosis and the exclusion of patients at increased bleeding risk, may have contributed to a lower incidence of thrombotic events than has been reported previously.[32] Although the platforms varied slightly in their classification of illness severity, the majority of patients who were receiving organ support at baseline were included in the analysis involving patients with severe disease.[19] Because we did not have detailed screening data, we were not able to specify the most common reasons for exclusion from the trial, other than a high bleeding risk or a clinical indication for anticoagulation. Thus, it is not possible to fully assess the generalizability of our findings. Finally, the treatment effect was attenuated in the final analysis relative to the adaptive stopping results; nevertheless, a high probability of benefit persisted.

Among noncritically ill patients hospitalized with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival until hospital discharge with reduced use of ICU-level organ support as compared with usual-care thromboprophylaxis.

The views expressed in this article are those of the authors and do not necessarily reflect the view of the National Health Service (in the United Kingdom [U.K.]), the U.K. National Institute for Health Research, the U.K. Department of Health and Social Care, or the National Institutes of Health in the United States.

The ATTACC platform was supported by grants from the Canadian Institutes of Health Research, LifeArc Foundation, Thistledown Foundation, Research Manitoba, Ontario Ministry of Health, Peter Munk Cardiac Centre, CancerCare Manitoba Foundation, and Victoria General Hospital Foundation. The ACTIV-4a platform was sponsored by the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH) (grant numbers, OTA-20-011 and 1OT2HL156812-01). The pilot program (PROTECT) was funded in part by a grant (UL1TR001445) from the New York University Clinical and Translational Science Award program, supported by the National Center for Advancing Translational Sciences of the NIH. The REMAP-CAP platform was supported by the European Union through FP7-HEALTH-2013-INNOVATION: the Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) consortium (602525) and the Horizon 2020 research and innovation program: the Rapid European Covid-19 Emergency Research response (RECOVER) consortium (101003589); by the Australian National Health and Medical Research Council (APP1101719 and APP1116530), the Health Research Council of New Zealand (16/631), the Canadian Institutes of Health Research (Strategy for Patient-Oriented Research Innovative Clinical Trials Program Grant [158584] and Covid-19 Rapid Research Operating Grant [447335]), the U.K. National Institute for Health Research (NIHR) and the NIHR Imperial Biomedical Research Centre, the Health Research Board of Ireland (CTN 2014-012), the Learning While Doing Program at the University of Pittsburgh Medical Center, the Breast Cancer Research Foundation, the French Ministry of Health (PHRC-20-0147), the Minderoo Foundation, Amgen, Eisai, the Global Coalition for Adaptive Research, and the Wellcome Trust Innovations Project (215522). Dr. Goligher is the recipient of an Early Career Investigator award from the Canadian Institutes of Health Research (grant AR7-162822). Dr. Gordon is supported by an NIHR Research Professorship (RP-2015-06-18), Dr. Shankar-Hari by an NIHR Clinician Scientist Fellowship (CS-2016-16-011), and Dr. Turgeon by a Canada Research Chair (Tier 2). Dr. Zarychanski is the recipient of the Lyonel G. Israels Research Chair in Hematology (University of Manitoba).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families who participated in this trial and the members of the data and safety monitoring board for each platform.

APPENDIX

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