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Symptoms and Impaired Quality of Life After COVID-19 Hospitalization: Effect of Therapeutic Heparin in Non-ICU Patients in the Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 Acute Trial

Effect on 3-Month Symptoms and Quality of Life

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BACKGROUND: Therapeutic-dose heparin decreased days requiring organ support in non-critically ill patients hospitalized for COVID-19, but its impact on persistent symptoms or quality of life (QOL) is unclear.

RESEARCH QUESTION: In the Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE (ACTIV-4a) trial, was randomization of patients hospitalized for COVID-19 illness to therapeutic-dose vs prophylactic heparin associated with fewer symptoms and better QOL at 90 days?

STUDY DESIGN AND METHODS: This was an open-label randomized controlled trial at 34 hospitals in the United States and Spain. A total of 727 noncritically ill patients hospitalized for COVID-19 from September 2020 to June 2021 were randomized to therapeutic-dose vs prophylactic heparin. Only patients with 90-day data on symptoms and QOL were analyzed. We ascertained symptoms and QOL by the EQ-5D-5L at 90-day follow-up in a preplanned analysis for the ACTIV-4a trial. Individual domains assessed by the EQ-5D-5L included mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Univariate and multivariate analyses were performed.

RESULTS: Among 571 patients, 288 (50.4%) reported at least one symptom. Among 410 patients, 148 (36.1%) reported moderate to severe impairment in one or more domains of the EQ-5D-5L. The presence of 90-day symptoms was associated with moderate-severe impairment in the EQ-5D-5L domains of mobility (adjusted OR [aOR], 2.37; 95% CI, 1.22-4.59), usual activities (aOR, 3.66; 95% CI, 1.75-7.65), pain (aOR, 2.43; 95% CI, 1.43-4.12), and anxiety (aOR, 4.32; 95% CI, 2.06-9.02), compared with patients reporting no symptoms There were no differences in symptoms or in the overall EQ-5D-5L index score between treatment groups. Therapeutic-dose heparin was associated with less moderate-severe impairment in all physical functioning domains (mobility, self-care, usual activities) but was independently significant only in the self-care domain (aOR, 0.32; 95% CI, 0.11-0.96).

INTERPRETATION: In a randomized controlled trial of hospitalized noncritically ill patients with COVID-19, therapeutic-dose heparin was associated with less severe impairment in the self-care domain of EQ-5D-5L. However, this type of impairment was uncommon, affecting 23 individuals.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov; No.: NCT04505774; URL: www.clinicaltrials.gov

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KEY WORDS: anticoagulation; COVID-19; heparin; quality of life

Take-home Points

Study Question: In the Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE trial, was randomization of patients hospitalized for COVID-19 to therapeutic-dose vs prophylactic heparin associated with fewer symptoms and better quality of life at 90 days?

Results: There were no differences in symptoms or the overall EQ-5D-5L index score between treatment groups. Therapeutic-dose heparin was associated with less moderate-severe impairment in all physical functioning domains (mobility, self-care, usual activities) but was independently significant only in the self-care domain.

Interpretation: Therapeutic-dose heparin is associated with less severe impairment in the self-care domain of the EQ-5D-5L. However, this type of impairment was uncommon, affecting 23 individuals.

Persistent symptoms and reduced quality of life (QOL) are common in critically ill and noncritically ill patients after infection with SARS-CoV-2.[1-9] The World Health Organization defines the postacute sequelae of COVID-19 infection (PASC), also known as long COVID or the post-COVID-19 condition, as symptoms that last for at least 2 months after an acute SARS-CoV-2 infection.[10] In one study from Italy, 63% of patients assessed at a mean of 60 days after the onset of PASC symptoms reported reduced QOL as measured with the EQ-5D-5L.[3] In an observational cohort study of 1,272 patients from China, 49% had at least one symptom 12 months after hospital discharge.[1]

In an international multiplatform randomized controlled trial (mpRCT) enrolling hospitalized patients with COVID-19, therapeutic-dose heparin increased the probability of survival without needing ICU-level organ support and the probability of survival to hospital discharge in noncritically ill patients hospitalized for COVID-19.[11] Benefits were not observed if patients were critically ill at baseline.[12] Whether these benefits in noncritically ill patients translate to improvement in 3-month patient-reported QOL and function is unknown.

To examine long-term outcomes, one of the participating platforms from the mpRCT, Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE (ACTIV-4a), had collected patient-reported symptoms and QOL data with the EQ-5D-5L 90 days after randomization. We hypothesized that randomization to therapeutic-dose heparin would be associated with fewer symptoms and less impairment of QOL compared with pharmacologic venous thromboprophylaxis.

Study Design and Methods

Patients

ACTIV-4a consisted of 34 sites that enrolled 779 patients into the mpRCT (e-Appendix 1 in the online article). Patients were randomized if they were admitted to a hospital for COVID-19, were within 72 h of hospital admission or in-hospital confirmation of a positive test result, and were expected to be hospitalized for at least 72 h (e-Appendix 2). Patients with an indication or contraindication for therapeutic-dose heparin or need for dual antiplatelet therapies

ABBREVIATIONS: ACTIV-4a = Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE; aOR = adjusted OR; mpRCT = multiplatform randomized controlled trial; PASC = postacute sequelae of COVID-19 infection; QOL = quality of life; VAS = visual analog scale

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were excluded. Further details regarding inclusion and exclusion criteria and platform harmonization are available in the original publication.[11] Patients were randomized to therapeutic-dose heparin vs usual care with either low-molecular-weight heparin or unfractionated heparin, administered according to local protocols and practice.[11]

This article focuses on the noncritically ill patients enrolled in ACTIV-4a who were not receiving ICU-level care at enrollment. The ICU level of care was defined as the use of cardiovascular (vasopressors or inotropes) or respiratory organ support (high-flow nasal cannula, invasive or noninvasive mechanical ventilation). Only patients who survived to 90 days and had completed a symptoms survey were included in this analysis. The EQ-5D-5L was added to data collection after enrollment, pending licensing. Once approved, all patients who completed the symptoms survey also completed the EQ-5D-5L.

The trial was approved by the relevant ethics committees (Western Institutional Review Board, IRB Registration No. IRB00000533) and conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonization. All the patients or their surrogates provided written or oral informed consent, in accordance with regional regulations.

90-Day Follow-Up Assessments

Follow-up of surviving patients was by telephone. Patients were queried regarding the presence of symptoms (cough, dyspnea at rest or with exertion, chest pain or tightness, feeling tired or lack of energy, and cognitive impairment). A symptom burden score was defined as the total number of these symptoms reported (0-6). Once the license was obtained, patient-reported QOL was added to the 90-day telephone call, using the EQ-5D-5L.[13] The EQ-5D-5L was assessed globally and by individual domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each domain patients answered a question regarding their level of impairment, ranging from no impairment to severe impairment or inability to do a task. For example, the mobility domain includes questions about problems in "walking about," with response options that include no problems, slight problems, moderate problems, severe problems, and inability to walk. For the visual analog scale (VAS), patients report their perceived health status from 0 to 100 on a VAS, where 0 is the worst possible health and 100 is the best possible health. The EQ-5D-5L index converts 3,125 unique health states from the domains described above into an index score ranging from 0 (death) to 1 (perfect health). Organ support was defined as the new use of high-flow oxygen, noninvasive and invasive mechanical ventilation, dialysis, extracorporeal membrane oxygenation, and vasopressor after enrollment any time within the first 21 days after randomization.

Statistical Analysis

We compared patient-reported symptom and QOL outcomes by treatment using the χ^2 test, Fisher exact test, or Wilcoxon rank-sum test, as appropriate. Specifically, we compared symptom burden (cough, dyspnea at rest or with exertion, chest pain or tightness, feeling tired or lack of energy, or cognitive impairments), and QOL determined by EQ-5D-5L, globally by VAS and EQ-5D-5L index, and by individual domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Patient responses to domain questions were then grouped into two categories: (1) less than moderate impairment, which included no impairment and slight impairment; and (2) moderate-severe impairment, which included impairment that ranges from moderate to severe, including the inability to perform a given domain task. Given that therapeutic heparin was found to reduce days requiring organ support, we also evaluated the relationship between organ support and symptoms and EQ-5D-5L as a secondary analysis.

Logistic regression was used for binary outcomes and linear regression for continuous outcomes. EQ-5D-5L models were adjusted for age, sex, residence in nursing home or other hospital facility other than home before admission, and baseline malignancy. Baseline malignancy was added to the adjusted models because it was not balanced by the treatment groups (Table 1). All statistical analyses were performed with Statistical Analysis Systems statistical software package 9.4 (SAS Institute).

Results

Patient Population

The trial was stopped on January 22, 2021, when the therapeutic-dose heparin met the predefined probability stopping threshold for superiority. The ACTIV-4a platform randomized 779 moderately ill patients hospitalized for COVID-19 out of the total of 2,244 patients enrolled in the multiplatform trial, and 727 had a planned 90-day follow-up. At 90 days, 91.2% (n = 663) were alive and five withdrew from the study and follow-up. Among the 658 patients who survived to 90 days and agreed to follow-up, 571 (87%) provided symptom data and 410 (62%) provided EQ-5D-5L data (Fig 1) and were included in the analysis of each outcome. Compared with those with 90-day data, patients missing data on symptoms were more likely to have unknown employment status, unknown health insurance status, and unknown location at 90 days, and were less likely to have received anticoagulation therapies before trial enrollment (e-Table 1). Patients missing EQ-5D-5L data were more likely to have unknown employment status and unknown race, to reside at an unknown location at 90 days, and to have no baseline oxygen requirements (e-Table 2). Age, sex, and preexisting medical conditions were well balanced between these groups for both 90-day symptoms and EQ-5D-5L data, and there was no difference in response rate to symptoms or EQ-5D-5L by treatment group.

Baseline and Hospitalization Characteristics

Baseline characteristics of the 571 patients with symptoms data at 90 days (289 patients randomized to therapeutic-dose heparin and 282 randomized to prophylactic-dose heparin) are shown in Table 1. The median age was 61 years and characteristics were similar by treatment group. During the hospital stay similar proportions in each group required organ support.

TABLE 1] Baseline Characteristics and Hospital Outcomes by Treatment Assignment (N = 571)

Characteristic	Therapeutic-Dose Heparin (n = 289)	Prophylactic-Dose Heparin (n = 282)
Site, No. (%)		
Spain	65 (17.9)	64 (17.6)
United States	299 (82.1)	299 (82.4)
Age, median (25th, 75th quartile), y	60.0 (50.0, 69.0)	60.0 (53.0, 69.0)
Sex		
Male	218 (59.9)	212 (58.4)
Female	146 (40.1)	151 (41.6)
Race, No. (%)		
White	206 (69.8)	214 (75.9)
Black	61 (20.7)	45 (16.0)
Other[a]	28 (9.5)	23 (8.2)
Ethnicity, No. (%)		
Non-Hispanic	222 (64.7)	225 (64.8)
Hispanic	121 (35.3)	122 (35.2)
Employment status, No. (%)		
Unemployed	32 (13.7)	42 (18.6)
Employed[b]	118 (50.6)	109 (48.2)
Retired	83 (35.6)	75 (33.2)
Health insurance status, No. (%)		
National/private health insurance	109 (42.1)	107 (40.8)
Medicare/Medicaid	136 (52.5)	135 (51.5)
Self-insured	14 (5.4)	20 (7.6)
Residence before admission, No. (%)		
Nursing facilities[c]	14 (3.9)	6 (1.7)
Home or similar location[d]	350 (96.2)	357 (98.4)
Preexisting medical conditions,[e] No. (%)		
Hypertension	203 (55.8)	189 (52.1)
Diabetes[f]	109 (30.0)	122 (33.6)
Chronic kidney disease[g]	33 (9.1)	34 (9.4)
Malignancy[h]	6 (1.7)	19 (5.2)
Immunosuppressive disease[i]	29 (8.0)	40 (11.0)
Smoking status, No. (%)		
Never	205 (60.8)	218 (64.5)
Ever[j]	132 (39.2)	120 (35.5)
Baseline treatment,[k] No. (%)		
Antiplatelet agents[l]	108 (29.7)	107 (29.5)
Anticoagulant therapies	282 (77.5)	281 (77.4)
Steroids	298 (81.9)	294 (81.0)
Remdesivir	238 (65.4)	250 (68.9)
Oxygen therapy used at baseline, No. (%)		
No oxygen therapy required	74 (20.3)	67 (18.5)
Low-flow nasal cannula/mask[m]	286 (78.6)	293 (80.7)
High-flow nasal cannula	4 (1.1)	3 (0.8)
Clinical measures		
BMI, kg/m^2, No. (%)		

(Continued)

TABLE 1] *(Continued)*

Characteristic	Therapeutic-Dose Heparin (n = 289)	Prophylactic-Dose Heparin (n = 282)
Normal weight (18.5-24.9)	52 (14.4)	60 (16.8)
Underweight (< 18.5)	6 (1.7)	2 (0.6)
Overweight (25.0-29.9)	126 (34.9)	114 (31.8)
Obese (≥ 30)	177 (49.0)	182 (50.8)
D-dimer level relative to ULN, median (25th, 75th quartile)	1.6 (1.0, 2.6)	1.6 (1.1, 2.7)
D-dimer, median (25th, 75th quartile), μg/L (FEU)	900 (578, 1,476)	892 (590, 1,495)
Creatinine, median (25th, 75th quartile)	0.9 (0.8, 1.1)	0.9 (0.7, 1.1)
WBC count, median (25th, 75th quartile)	6.6 (4.6, 8.8)	6.2 (5.0, 8.5)
CRP, median (25th, 75th quartile)	84.6 (47.0, 133.4)	74.1 (42.7, 126.0)
Hospital outcomes		
90-d survival, No. (%)	334 (91.8)	329 (90.6)
Rehospitalization, No. (%)[n]	23 (6.3)	28 (7.7)
Residence after discharge, No. (%)	345	344
Nursing facilities[c]	22 (6.4)	22 (6.4)
Home or similar location[d]	323 (93.6)	322 (93.6)
Residence at 90 d, No. (%)	307	294
Nursing facilities[c]	11 (3.6)	9 (3.1)
Home or similar location[d]	296 (96.4)	285 (96.9)
Receipt of organ support, days 0-21, No. (%)		
Did not receive any organ support	284 (83.3)	285 (84.1)
Received any organ support	57 (16.7)	54 (15.9)

CRP = C-reactive protein; FEU = fibrinogen equivalent unit; ULN = upper limit of normal.
[a]Other: Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Aboriginal/First Nations, Other, Multiracial.
[b]Employed: Student, employee, employer, own-account worker, member of producers' cooperatives, contributing family worker, worker not classifiable by status.
[c]Nursing facilities: Nursing home, rehabilitation facility, another acute care hospital.
[d]Home or similar location: Home, hotel/temporary housing, homeless, other.
[e]Participants with missing data for preexisting medical conditions were treated as not having the conditions.
[f]Diabetes: Type 1 diabetes, type 2 diabetes.
[g]Chronic kidney disease (CKD): CKD not on dialysis and CKD on dialysis.
[h]Malignancy: Acute leukemia, lymphoma, metastatic cancer, myeloma, malignancy receiving chemotherapy.
[i]Immunosuppressive disease: HIV, autoimmune disease, transplant recipient.
[j]Ever: Former, Current.
[k]Patients with missing data for baseline treatments were treated as not receiving the treatments.
[l]Antiplatelet agents: Aspirin, other antiplatelet agents.
[m]Low-flow nasal cannula/mask: Nasal cannula, venturi mask, face mask with oxygen reservoir.
[n]Rehospitalization was assessed 28 days after randomization.

Symptoms and Quality of Life at 90 Days

At 90 days, similar proportions in each treatment group were readmitted, or resided at a location other than home at either discharge or 90 days (Table 1).

Symptoms were common at 90-day follow-up with 288 patients (50.4%) reporting at least one symptom and 159 (28%) reporting two or more persistent symptoms. The most common symptoms reported were respiratory symptoms including dyspnea on exertion and cough (n = 286, 50.1%) and fatigue (n = 211, 37.5%) (Figs 2A and 2B). e-Table 3 shows the association of patient characteristics with prevalence of one or more symptoms at 90 days. Female patients were more likely to report symptoms (47.3% vs 37.3% among those without symptoms). Patients residing at a nursing facility before admission were more likely to report symptoms (3.8% vs 0.4% among those without symptoms). There was no difference in reported symptoms between patients who required organ support during enrollment and those who did not.

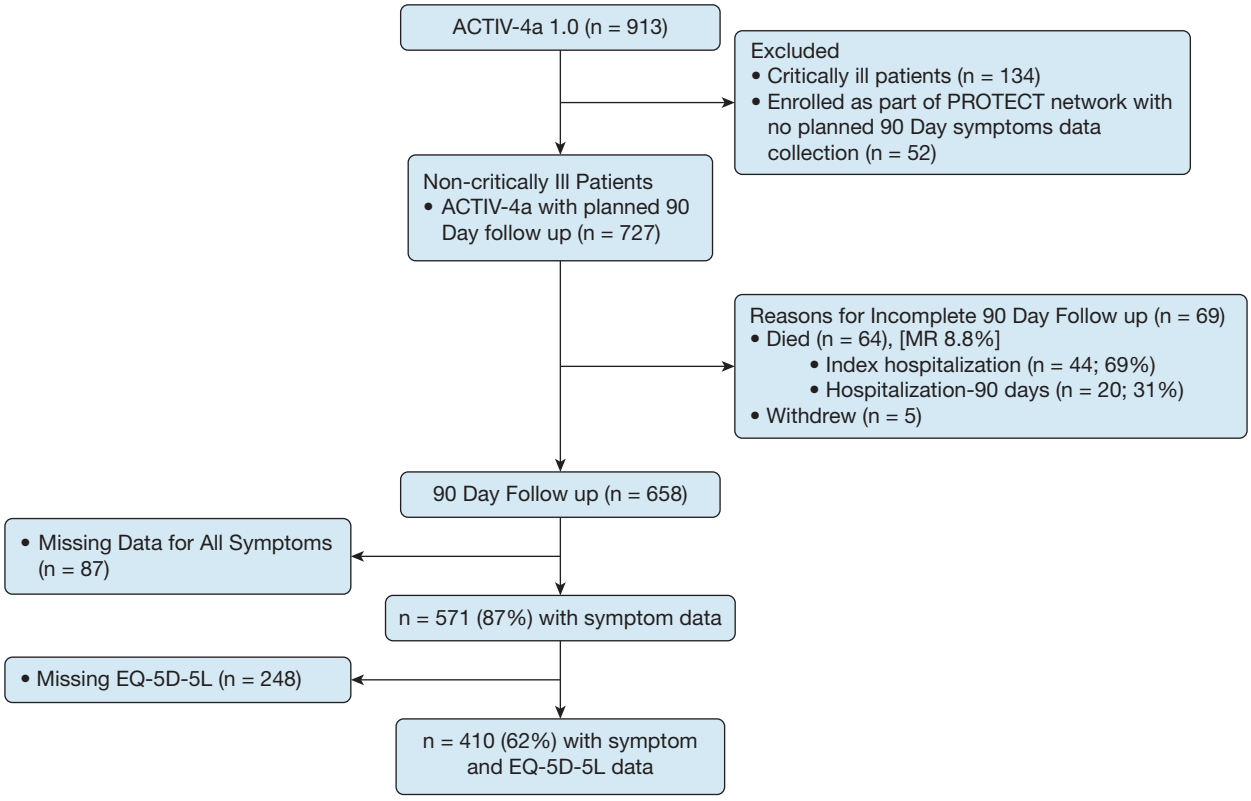

Figure 1 – *Enrollment and inclusion in analysis. Patients from the ACTIV-4a clinical trial were identified for this analysis. Only noncritically ill patients alive at 90 days with symptom data (571) were included in the analysis. ACTIV-4a = Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE. MR = mortality rate; PROTECT = Prophylaxis for Thromboembolism in Critical Care Trial.*

The median EQ-5D-5L VAS and index scores were 80 (25th, 75th quartile, 70-90) and 0.932 (25th, 75th quartile, 0.776-1), respectively (Table 2). In unadjusted linear regression, there were no associations of randomized treatment assignment with either outcome (Table 3). Worse VAS scores were observed among female patients; residents at a nursing home or facility before admission and at 90 days; and among those with diabetes, chronic kidney disease, and preexisting malignancy. Similar results were found for EQ-5D-5L index scores except that older age, unemployment status, and preadmission antiplatelet use were also associated with worse index score.

The need for organ support during the index hospitalization was not associated with VAS or EQ-5D-5L index scores (VAS: β, –0.59; SE, 2.48; $P = .81$; index: β, 0.83; SD, 0.25; $P = .90$). A total of 148 (36.1%) reported at least moderate to severe impairment in one or more domains. Moderate to severe impairment was reported by 54 patients (13.2%) in the domain of mobility, 23 patients (5.6%) in self-care, 55 patients (13.5%) in usual activities, 97 patients (23.7%) in the pain/discomfort domain, and 61 patients (14.9%) in the anxiety/depression domain (Fig 2C). Patients who needed organ support more commonly reported impairments in the physical functioning domains of usual activities, mobility, and self-care that was statistically significant only in the domain of usual activities ($P = .03$) (e-Fig 1). Need for organ support was not associated with increased impairment in the domains of pain/discomfort and anxiety/depression.

Baseline factors associated with moderate to severe impairment in each QOL domain are listed in e-Table 4. Compared with male participants, female participants had significantly greater impairment across all domains on the EQ-5D-5L except the mobility domain. Several factors were associated with moderate to severe impairment in the physical domains of mobility, self-care, or usual activities. For self-care these included retirement, Medicare or Medicaid insurance, prehospital residence in nursing home or facilities, residing in the United States compared with Spain, preexisting hypertension, diabetes, chronic kidney disease, preexisting immunosuppressive disease,

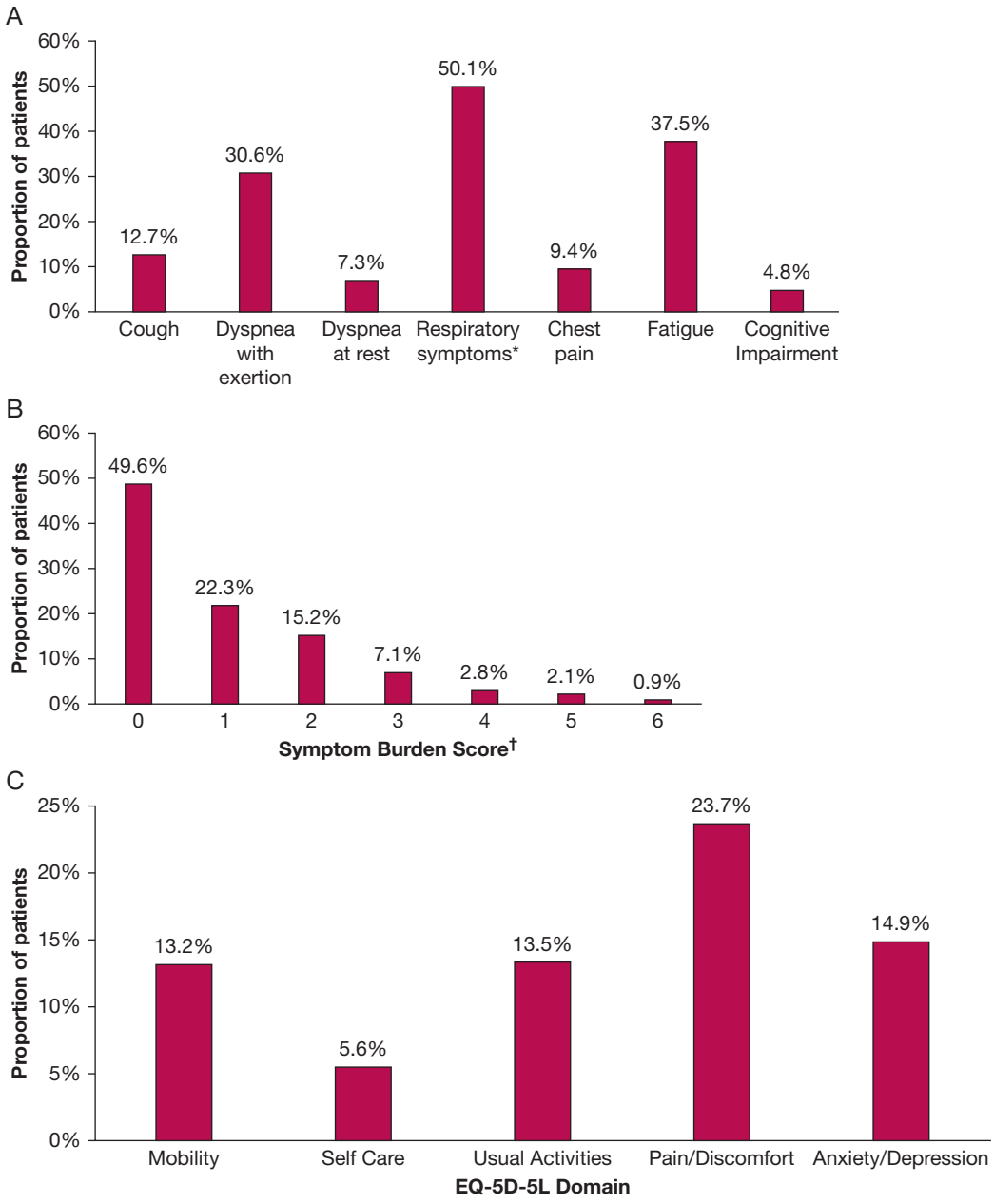

Figure 2 – *A-C, Patient-reported symptoms and moderate to severe impairment in EQ-5D-5L at 90 days. A, The proportion of patients reporting any symptoms at 90 days after enrollment. Respiratory symptoms* were the most commonly reported. B, Proportion of patients by symptom burden score† at 90 days after enrollment with 23.4% of patients reporting at least one symptom at 90 days. C, Proportion of patients reporting at least moderate impairment in the EQ-5D-5L domains at 90 days. *Respiratory symptoms are a composite of cough, dyspnea with exertion, and dyspnea at rest. †Symptom burden score was defined as the total number of the following symptoms: cough, dyspnea with exertion, dyspnea at rest, chest pain or tightness, feeling tired or lack of energy, and cognitive impairment.*

and malignancy. In the nonphysical function domains, patients with preexisting malignancy were more likely to report impairment in the pain/discomfort domain (7.2% vs 1.9%; $P = .02$). Obesity was associated with greater impairment in pain/discomfort (62.1% vs 46.5%; $P = .03$), and greater impairment in anxiety/depression (68.9% vs 46.8%; $P = .01$). Antiplatelet therapies during hospitalization were associated with more moderate to severe impairment in the self-care domain (47.8% vs 24.6%; $P = .01$) whereas treatment with remdesivir was associated with less moderate to severe impairment in usual activities (56.4% vs 70.1%; $P = .04$).

The presence of any symptoms was associated with worse QOL by EQ-5D-5L VAS (adjusted OR [aOR], 0.95; 95% CI, 0.95-0.97) and EQ-5D-5L index (aOR,

TABLE 2] Impairment and Quality of Life Measured by EQ-5D-5L Overall and by Treatment in ACTIV-4a Moderate Cohort

Quality of Life Indicators	Overall (n = 410)	Therapeutic-Dose Heparin (n = 209)	Prophylactic-Dose Heparin (n = 201)	*P* Value
EQ-5D-5L domain				
Mobility, No. (%)				.30
< Moderate impairment[a]	356 (86.8)	185 (88.5)	171 (85.1)	
≥ Moderate impairment[b]	54 (13.2)	24 (11.5)	30 (14.9)	
Self-care, No. (%)[c]				.02
< Moderate impairment[a]	386 (94.4)	202 (97.1)	184 (91.5)	
≥ Moderate impairment[b]	23 (5.6)	6 (2.9)	17 (8.5)	
Usual activity, No. (%)[d]				.08
< Moderate impairment[a]	354 (86.6)	186 (89.4)	168 (83.6)	
≥ Moderate impairment[b]	55 (13.5)	22 (10.6)	33 (16.4)	
Pain/discomfort, No. (%)[e]				.55
< Moderate impairment[a]	312 (76.3)	162 (77.5)	150 (75.0)	
≥ Moderate impairment[b]	97 (23.7)	47 (22.5)	50 (25.0)	
Anxiety/depression, No. (%)[f]				.82
< Moderate impairment[a]	348 (85.1)	177 (84.7)	171 (85.5)	
≥ Moderate impairment[b]	61 (14.9)	32 (15.3)	29 (14.5)	
EQ-5D-5L VAS, median (25th, 75th quartile)[g]	80 (70, 90)	80 (70, 90)	80 (70, 90)	.61
EQ-5D-5L index score, median (25th, 75th quartile)	0.932 (0.776, 1)	0.94 (0.779, 1)	0.904 (0.734, 1)	.19

ACTIV-4a = Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE; VAS = visual analog scale.
[a]Moderate impairment includes score of 1 or 2 on EQ-5D domain.
[b]≥ Moderate impairment includes score of 3, 4, or 5 on EQ-5D domain.
[c]Missing data from one patient in the therapeutic-dose heparin group.
[d]Missing data from one patient in the therapeutic-dose heparin group.
[e]Missing data from one patient in the prophylactic-dose heparin group.
[f]Missing data from one patient in the prophylactic-dose heparin group.
[g]Missing data from five patients in the therapeutic-dose heparin group and three patients in the prophylactic-dose heparin group.

0.11; 95% CI, 0.03-0.38) (e-Table 5). Adjusting for age, sex, residence before admission, and chronic kidney disease, patients reporting any symptoms were more likely to report moderate-severe impairment on the EQ-5D-5L in mobility (aOR, 2.37; 95% CI, 1.22-4.59), usual activities (aOR, 3.66; 95% CI, 1.75-7.65), pain/discomfort (aOR, 2.43; 95% CI, 1.43-4.12), and anxiety/depression (aOR, 4.32; 95% CI, 2.06-9.02).

Therapeutic-Dose Heparin, Symptoms, and Quality of Life at 90 Days

There were no differences in the distribution of symptoms or symptom burden score at 90 days between treatment groups (e-Fig 2). In multivariable analysis adjusted for age, sex, and residence before admission, there was no difference in the presence of any symptoms at 90 days by treatment group (aOR comparing therapeutic with prophylactic anticoagulation, 1.19; 95% CI, 0.85-1.66; $P = .30$).

Randomization to therapeutic-dose heparin was associated with less moderate to severe impairment in the self-care domain (26.1% vs 73.9%; $P = .01$). On multivariable analysis adjusting for age, sex, residence before admission, and malignancy, therapeutic-dose heparin remained significantly associated with less moderate to severe impairment in the self-care domain (aOR, 0.32; 95% CI, 0.11-0.96; $P = .02$) (Fig 3). In the adjusted models, therapeutic-dose heparin also had lower rates of moderate-severe impairment in the other quality of life domains, but these differences were not statistically significant. There were no differences between treatment groups in the EQ-5D-5L VAS and EQ-5D-5L index (VAS: β, –0.06; SE, 1.70; $P = .97$; index: β, 0.036; SE, 0.03; $P = .18$) (e-Table 6).

TABLE 3] Associations of Patient Characteristics With EQ-5D-5L VAS and EQ-5D-5L Index in ACTIV-4a Moderate Cohort

Characteristic	EQ-5D-5L VAS (n = 402)		EQ-5D-5L Index (n = 326)	
	Mean (SD)	*P* Value[a]	Mean (SD)	*P* Value[a]
Site		.5632		N/A
Spain	79.02 (15.52)		USA only	
USA	77.79 (17.63)		…[b]	
Age, y, PC	−0.0410	.4120	−0.1492	.0069
Sex		.0034		.0182
Male	80.18 (16.02)		0.86 (0.25)	
Female	75.1 (18.39)		0.79 (0.24)	
Race[c]		.9767		.3314
White	77.76 (17.4)		0.82 (0.27)	
Black	77.19 (18.66)		0.8 (0.25)	
Other[d]	77.59 (18.42)		0.9 (0.16)	
Ethnicity[e]		.9075		.0941
Non-Hispanic	77.94 (17.19)		0.84 (0.23)	
Hispanic	77.73 (17.3)		0.79 (0.29)	
Employment status[f]		.0044		.0007
Unemployed	75.38 (15.83)		0.76 (0.33)	
Employed[g]	81.16 (15.84)		0.89 (0.17)	
Retired	73.88 (18.43)		0.75 (0.28)	
Health insurance status[h]		.0052		.0172
National/private health insurance	80.73 (15.6)		0.86 (0.22)	
Medicare/Medicaid	74.39 (17.39)		0.79 (0.27)	
Self-insured	81.56 (15.46)		0.93 (0.09)	
Residence before admission		.0448		.0190
Home or similar location[i]	78.3 (16.94)		0.83 (0.24)	
Nursing facilities[j]	66.67 (25.25)		0.63 (0.38)	
Residence after discharge[k]		.9181		.0274
Home or similar location[l]	78.31 (17.01)		0.84 (0.23)	
Nursing facilities or hospice[m]	77.89 (15.63)		0.71 (0.37)	
Residence at 90 d		.0002		< .0001
Home or similar location[l]	78.52 (16.68)		0.84 (0.23)	
Nursing facilities or hospice[m]	57.22 (26.71)		0.38 (0.34)	
Preexisting medical conditions[n]				
Hypertension	76.5 (16.96)	.0664	0.81 (0.25)	.2171
Diabetes[o]	74.71 (16.71)	.0127	0.79 (0.27)	.0747
Chronic kidney disease[p]	71.15 (20.16)	.0347	0.71 (0.33)	.0094
Malignancy[q]	63.67 (30.68)	.0032	0.66 (0.4)	.0100
Immunosuppressive disease[r]	73.66 (16.29)	.1148	0.79 (0.23)	.3058
Smoking status[s]		.4398		.6063
Never	78.62 (17.19)		0.83 (0.24)	
Ever[t]	77.21 (17.21)		0.82 (0.26)	
Baseline treatment[u]				
Antiplatelet agents[v]	76.32 (17.1)	.2396	0.79 (0.28)	.0360
Anticoagulant therapies	77.92 (18.01)	.7969	0.83 (0.26)	.7339

(Continued)

TABLE 3] *(Continued)*

Characteristic	EQ-5D-5L VAS (n = 402)		EQ-5D-5L Index (n = 326)	
	Mean (SD)	*P* Value[a]	Mean (SD)	*P* Value[a]
Steroids	78.42 (16.5)	.3830	0.84 (0.24)	.2530
Remdesivir	78.57 (17.38)	.3789	0.84 (0.24)	.1254
Oxygen therapy used at baseline visit		.0266		.3839
No oxygen therapy required	73.12 (17.53)		0.8 (0.26)	
Low-flow nasal cannula/mask[w]	78.91 (17.07)		0.83 (0.25)	
High-flow nasal cannula	88.33 (2.89)		0.97 (0.06)	
Clinical measures				
BMI[x]		.0636		.0192
Normal weight (18.5-24.9)	76.53 (19.47)		0.8 (0.29)	
Underweight (< 18.5)	63.33 (23.09)		0.61 (0.54)	
Overweight (25.0-29.9)	80.8 (15.87)		0.89 (0.17)	
Obese (≥ 30)	76.68 (17.11)		0.81 (0.26)	
D-dimer level relative to ULN,[y] PC	0.0516	.3760	0.0042	.9459
Creatinine,[z] PC	0.0168	.7402	0.0221	.6955
WBC count, PC	0.0342	.4937	0.0295	.5952
CRP,[aa] PC	−0.0551	.3564	0.0317	.6494
Treatment arm		.9429		.1266
Prophylactic-dose heparin	77.98 (18.26)		0.81 (0.27)	
Therapeutic-dose heparin	78.1 (16.18)		0.85 (0.22)	
Receipt of organ support days 0-21		.8127		.9002
Did not receive any organ support	78.12 (17.14)		0.83 (0.25)	
Received any organ support	77.54 (17.83)		0.83 (0.25)	

Data are reported as Mean (SD) unless otherwise noted. ACTIV-4a = Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE; CRP = C-reactive protein; N/A = not applicable; PC = Pearson correlation coefficient; VAS = visual analog scale.
[a]*P* values are determined using *t* tests if binary variable, analysis of variance if multicategorical, or Pearson correlation if continuous.
[b]EQ-5D-5L Index value was not available for Spain.
[c]VAS missing data (n = 63, 15.7%); EQ-5D missing data (n = 67, 20.6%).
[d]Other: Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Aboriginal/First Nations, other, multiracial.
[e]VAS missing data (n = 18, 4.5%); EQ-5D missing data (n = 16, 4.9%).
[f]VAS missing data (n = 139, 34.6%); EQ-5D missing data (n = 139, 42.6%).
[g]Employed: Student, employee, employer, own-account worker, member of producers' cooperatives, contributing family worker, worker not classifiable by status.
[h]VAS missing data (n = 120, 29.9%); EQ-5D missing data (n = 65, 19.9%).
[i]Home or similar location: Home, hotel/temporary housing, homeless, other.
[j]Nursing facilities: Rehabilitation facility, another acute care hospital.
[k]VAS missing data (n = 3, 0.7%); EQ-5D missing data (n = 3, 0.9%).
[l]Home or similar location: Discharged/at home, in hotel/temporary housing, homeless.
[m]Nursing facilities or hospice: Hospice, rehabilitation facility, facility providing organ support.
[n]Patients with missing data for preexisting medical conditions were treated as not having the conditions.
[o]Diabetes: Type 1 diabetes, Type 2 diabetes.
[p]Chronic kidney disease (CKD): CKD not on dialysis and CKD on dialysis.
[q]Malignancy: Acute leukemia, lymphoma, metastatic cancer, myeloma, malignancy receiving chemotherapy.
[r]Immunosuppressive disease: HIV, autoimmune disease, transplant recipient.
[s]VAS missing data (n = 29, 7.2%); EQ-5D missing data (n = 26, 8.0%).
[t]Ever: Former, Current.
[u]Patients with missing data for baseline treatments were treated as not receiving the treatments.
[v]Antiplatelet agents: Aspirin, Other antiplatelet agents.
[w]Low-flow nasal cannula/mask: Nasal cannula, venturi mask, face mask with oxygen reservoir.
[x]VAS missing data (n = 4, 1.0%); EQ-5D missing data (n = 1, 0.3%).
[y]VAS missing data (n = 106, 26.4%); EQ-5D missing data (n = 68, 20.9%).
[z]VAS missing data (n = 11, 2.7%); EQ-5D missing data (n = 11, 3.4%).
[aa]VAS missing data (n = 120, 29.9%); EQ-5D missing data (n = 118, 36.2%).

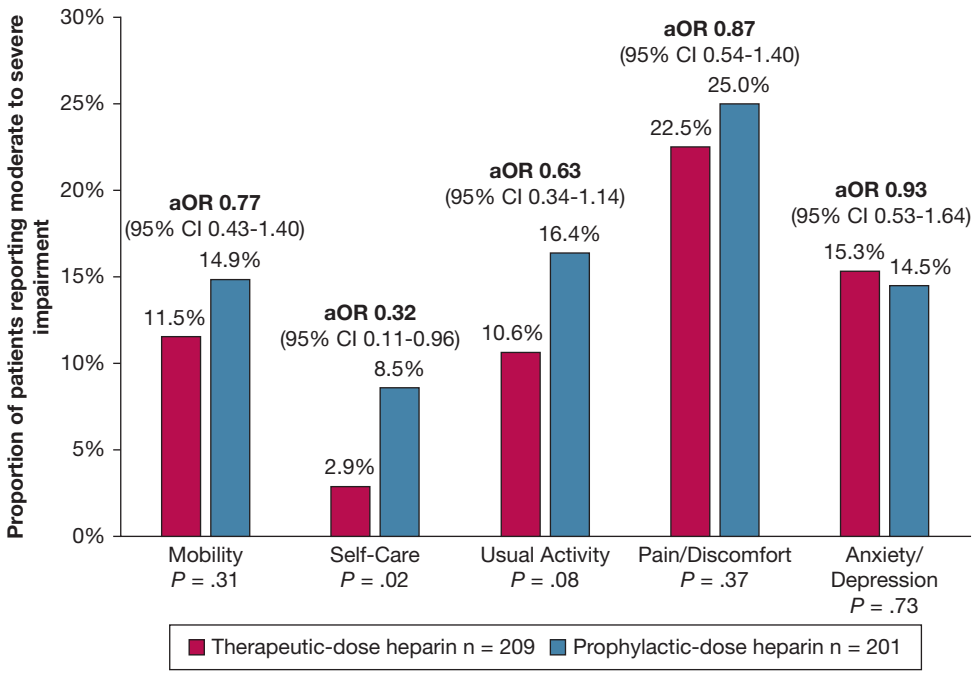

Figure 3 – *Adjusted ORs of moderate-severe impairment in EQ-5D-5L domains by treatment assignment in the ACTIV-4a moderate cohort. In the domain of self-care there was a significant reduction in the degree of impairment reported in patients who received therapeutic-dose heparin. There was a trend in both mobility and usual activity to reduced impairment in patients who received therapeutic-dose heparin. Logistic regressions were adjusted for, using age, sex, residence before admission, and malignancy. ACTIV-4a = Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE; aOR = adjusted OR.*

Discussion

In this randomized controlled trial of patients hospitalized for COVID-19, the burden of symptoms and moderate to severe impairment in QOL at 90 days was high even for these noncritically ill patients. Symptom burden correlated with worse QOL. The need for organ support during hospitalization did not significantly correlate with symptoms but did correlate with more impairment in the physical functioning domains of the EQ-5D-5L. Therapeutic-dose heparin was not associated with fewer symptoms at 90 days, symptom burden, or EQ-5D-5L VAS and index scores, but was associated with less moderate-severe impairment in the physical functioning domain of self-care.

Under the World Health Organization definition, more than one-half of the ACTIV4a trial patients surviving 90 days after discharge had PASC at 90 days. Similarly high rates of symptoms and reduced QOL have been reported in other cohorts, with respiratory symptoms and fatigue being the most common symptoms.[1,3,14-20] Risk factors associated with symptoms and lower QOL in this study are similar to those described in prior reports, with female patients more likely to report symptoms and worse QOL.[15,18,20] In general, there were more predictors for impairment in the physical function domains of the EQ-5D-5L than the pain, anxiety, and depression domains. Consistent with other studies, age, prior residence in a nursing home or other facility, and certain comorbidities were associated with worse physical functions in the EQ-5D-5L.[18,20,21] Only female sex, malignancy, and obesity were associated with pain or anxiety/depression.

In a recent report from Randomized Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia (REMAP-CAP), antiplatelet agents and IL-6 receptor antagonists, but not therapeutic-dose heparin, improved QOL at 180 days as measured by the EQ-5D-5L index.[22] Although REMAP-CAP did contribute to the mpRCT, that report concentrated on critically ill patients only in which antiplatelet agents and IL-6 receptor antagonists were found to improve 180-day mortality whereas therapeutic anticoagulation was not found to be beneficial. Our study focuses on the noncritically ill patients hospitalized for COVID-19 in which therapeutic anticoagulation was found to reduce the development and duration of organ failure compared with usual care thromboprophylaxis.[11] Our results suggest that therapeutic-dose heparin was associated

with reduced impairment in self-care at 90 days in a noncritically ill cohort, with a prevalence of moderate-severe impairment in 2.9% of patients assigned to therapeutic-dose heparin and 8.5% with prophylactic-dose heparin, and an aOR of moderate-severe impairment of 0.32 (95% CI, 0.11-0.96). There were smaller effects for other QOL impairments that were not statistically significant, and no association of treatment assignment with the presence of symptoms. Improved understanding of long-term effects of acute illnesses, such as sepsis and acute respiratory failure, is a research priority.[23] This is even more urgent given the high burden of symptoms and impairment reported after acute COVID-19.

The mechanism for the associations we observed is not clear. It is possible that attenuation of chronic endotheliopathy and coagulation activation are relevant, as these have been observed in PASC.[24,25] Therapeutic-dose heparin was not associated with reduced symptoms, whereas symptoms were associated with worse QOL. However, therapeutic-dose heparin did significantly decrease the development and duration of organ failure in noncritically ill patients in the larger mpRCT. Worse long-term physical and cognitive outcomes have been shown in prior studies on acute respiratory failure to be associated with greater severity of organ failure and illness during the acute illness.[26,27] Thus, one important strategy for preventing long-term sequelae after COVID-19 or other severe illness may be more effective treatment of the acute illness to prevent more severe disease. Indeed, a recent observational study from the US Veterans Administration showed that treatment with nirmatrelvir, which has been demonstrated to prevent hospitalization, was associated with lower risk of PASC.[28] Of note, our study also showed an association between less impairment in the usual activities domain of the EQ-5D-5L among patients treated with remdesivir, which was found to improve recovery from acute COVID-19 in hospitalized patients.[29] Together, these studies suggest that acute interventions that can prevent progression of COVID-19 to severe disease can ameliorate the long-term impact of the disease.

It is important to note that therapeutics that can improve short-term outcomes and organ failure may not necessarily improve long-term function and QOL. For example, although corticosteroids improve mortality and progression to mechanical ventilation from COVID-19 pneumonia in clinical trials,[30-34] they resulted in more myopathy, neuropathy, and fatigue in the long term in a clinical trial of ARDS[30,35] and were associated with worse physical function and QOL in a cohort of patients with COVID-19 1 year after illness.[1] Indeed, in critically ill patients in REMAP-CAP, corticosteroids were associated with more problems in the EQ-5D-5L domains of self-care and usual activities.[22] In contrast, in our study, therapeutic-dose heparin was independently significantly associated with less moderate-severe impairment in the self-care domain and was nonsignificantly associated with improvement in the other domains except anxiety/depression. This demonstrates the importance of embedding long-term outcomes and follow-up into acute-care clinical trials to determine the downstream effects of interventions during the acute phase.

Most findings of factors associated with QOL were notable in the domains of physical function rather than pain or anxiety/depression. This heterogeneous effect across the different domains may contribute to the lack of association found between therapeutic anticoagulation and the global assessment of QOL with the EQ-5D-5L VAS and index score. It is also possible that there are different drivers for different domains of QOL after COVID-19 infection. Given the isolation and economic consequences of the pandemic, it is likely that the hospitalized data collected in this trial do not adequately measure the social and environmental stresses that would contribute to these domains.

This study has several limitations. The sample size may not be powered enough to detect statistically significant differences in the QOL outcomes. Given that this analysis only included patients from ACTIV4a, the smaller patient population did not demonstrate as large a difference in organ support free days than the larger multiplatform trial, which could result in less difference in QOL between treatment arms. We had an 87% response rate for symptoms but only a 62% response rate for EQ-5D-5L because it was added later in the study after enrollment had begun as we were waiting for licensing. It is possible that we lacked sufficient power for some analyses, although we did not identify factors related to missing data that might bias the results. We did not account for the potential effect of multiple comparisons given our sample size, and thus the results should be considered exploratory. The reduction in impairment in the self-care domain shown in this study was reported in a total of 23 patients and could potentially represent a chance finding. Despite some missing data, this is the largest randomized trial of

noncritically ill patients with acute COVID-19 with long-term symptom and QOL outcomes to our knowledge. We did not examine the critically ill patients here because therapeutic-dose heparin was not found to be effective in that patient population. Long-term outcomes in critically ill patients were recently published.[22] We did not have a baseline assessment of symptoms and QOL before infection, so we cannot determine any change subsequent to acute COVID-19 infection. Indeed, patients who were missing symptoms or EQ-5D-5L data at 90 days were less likely to be employed, insured, or discharged to home, which would bias the study to underestimate symptoms and impairment in QOL. We do not report outcomes beyond 90 days, so total duration of symptoms and improvement in QOL over time were not determined. We had only English and Spanish versions of EQ-5D-5L, so the results may not be generalizable around the world. In addition, most patients were enrolled in this trial early in the pandemic, so the prevalence of symptoms, impairment of QOL, and effect of therapeutic-dose heparin on later variants such as Omicron were not studied.

This study has several strengths. Follow-up 90 days after enrollment was done prospectively to examine long-term outcome and recovery. By leveraging the randomization of therapeutic vs prophylactic-dose heparin, we provide a more robust examination of the effect of therapeutic-dose heparin on outcomes compared with observational studies. Whereas other studies on QOL and impairment focused on critically ill patients with COVID-19, this study focused on noncritically ill patients; this is relevant to a much larger number of patients hospitalized with COVID-19, for whom a high burden of symptoms and impairment is still reported.

The burden of symptoms and impairment in QOL measured at 90 days were high even among noncritically ill patients with acute COVID-19. Therapeutic-dose heparin compared with prophylactic-dose heparin was associated with less moderate to severe impairment in several physical functioning domains of the EQ-5D-5L especially in self-care. To our knowledge this is the first report of an acute intervention shown to be effective in a clinical trial for short-term outcomes to also reduce the possibility of PASC in noncritically ill patients with acute COVID-19. Our findings highlight the potential impact of acute interventions on PASC and might guide the design of future studies in this field.

Interpretation

Therapeutic-dose heparin is independently associated with less severe impairment in the self-care domain of EQ-5D-5L, but not with fewer symptoms at 90 days.

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Additional information: The e-Figures, e-Tables, and e-Appendixes are available online under "Supplementary Data."

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