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BRIEF REPORT

Effect of therapeutic-dose heparin on severe acute kidney injury and death in noncritically ill patients hospitalized for COVID-19: a prespecified secondary analysis of the ACTIV4a and ATTACC randomized trial

Nathaniel R. Smilowitz[1] | Erinn M. Hade[1] | Lucy Z. Kornblith[2] | Lana A. Castellucci[3,4] | Mary Cushman[5] | Michael Farkouh[6,7] | Michelle N. Gong[8,9] | Anna Heath[10] | Beverly J. Hunt[11] | Keri S. Kim[12] | Andrei Kindzelski[13] | Patrick Lawler[6,7] | David E. Leaf[14] | Ewan Goligher[7,15] | Eric S. Leifer[13] | Bryan J. McVerry[16,17] | Harmony R. Reynolds[1] | Ryan Zarychanski[18,19] | Judith S. Hochman[1] | Matthew D. Neal[16,17] | Jeffrey S. Berger[1]

[1]NYU Grossman School of Medicine, New York, New York, USA

[2]Zuckerberg San Francisco General Hospital, University of California, San Francisco, California, USA

[3]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

[4]University of Ottawa, Ottawa, Ontario, Canada

[5]Larner College of Medicine at the University of Vermont, Burlington, Vermont, USA

[6]Peter Munk Cardiac Centre at University Health Network, Toronto, Ontario, Canada

[7]University of Toronto, Toronto, Ontario, Canada

[8]Montefiore Medical Center, Bronx, New York, USA

[9]Albert Einstein College of Medicine, Bronx, New York, USA

[10]The Hospital for Sick Children, Toronto, Ontario, Canada

[11]Kings College, London, UK

[12]University of Illinois, Chicago, Illinois, USA

[13]National Heart Lung & Blood Institute, NIH, Bethesda, Maryland, USA

[14]Brigham and Women's Hospital Harvard Medical School, Boston, Massachusetts, USA

[15]University Health Network, Toronto, Ontario, Canada

[16]University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[17]UPMC, Pittsburgh, Pennsylvania, USA

[18]University of Manitoba, Winnipeg, Manitoba, Canada

[19]CancerCare Manitoba, Winnipeg, Manitoba, Canada

Correspondence
Jeffrey S. Berger, Center for the Prevention of Cardiovascular Disease, New York University School of Medicine, 530 First Avenue, Skirball 9R, New York, NY 10016, USA.
Email: jeffrey.berger@nyulangone.org

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Abstract

Background: Acute kidney injury (AKI) in patients with COVID-19 is partly mediated by thromboinflammation. In noncritically ill patients with COVID-19, therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support.

Objectives: We investigated whether therapeutic-dose heparin reduces the incidence of AKI or death in noncritically ill patients hospitalized for COVID-19.

Methods: We report a prespecified secondary analysis of the ACTIV4a and ATTACC open-label, multiplatform randomized trial of therapeutic-dose heparin vs usual-care pharmacologic thromboprophylaxis on the incidence of severe AKI (≥2-fold increase in serum creatinine or initiation of kidney replacement therapy (KDIGO stage 2 or 3) or all-cause mortality in noncritically ill patients hospitalized for COVID-19. Bayesian statistical models were adjusted for age, sex, D-dimer, enrollment period, country, site, and platform.

Results: Among 1922 enrolled, 23 were excluded due to pre-existing end stage kidney disease and 205 were missing baseline or follow-up creatinine measurements. Severe AKI or death occurred in 4.4% participants assigned to therapeutic-dose heparin and 5.5% assigned to thromboprophylaxis (adjusted relative risk [aRR]: 0.72; 95% credible interval (CrI): 0.47, 1.10); the posterior probability of superiority for therapeutic-dose heparin (relative risk < 1.0) was 93.6%. Therapeutic-dose heparin was associated with a 97.7% probability of superiority to reduce the composite of stage 3 AKI or death (3.1% vs 4.6%; aRR: 0.64; 95% CrI: 0.40, 0.99) compared to thromboprophylaxis.

Conclusion: Therapeutic-dose heparin was associated with a high probability of superiority to reduce the incidence of in-hospital severe AKI or death in patients hospitalized for COVID-19.

KEYWORDS
acute kidney injury, anticoagulants, COVID-19, death, heparin, kidney diseases, mortality

Essentials

- Acute kidney injury (AKI) occurs with COVID-19 and may be due to thromboinflammation.
- We evaluated blood thinner dose and kidney injury in hospitalized patients with COVID-19.
- Severe kidney injury or death occurred in 4.9% of participants with COVID-19.
- Therapeutic-dose heparin had a high probability of superiority of reducing AKI/death in COVID-19.

1 | INTRODUCTION

Acute kidney injury (AKI) occurs in patients with COVID-19 and may be partly mediated by thromboinflammation [1–4]. Heparin is associated with potentially advantageous antithrombotic and anti-inflammatory properties that may mitigate risks of AKI [5]. In noncritically ill patients with COVID-19, therapeutic-dose heparin increased the probability of survival in hospital discharge with reduced use of cardiovascular or respiratory organ support [6]. However, the effect of therapeutic-dose heparin on the incidence of COVID-19–associated AKI is unknown. A consensus statement from the Acute Disease Quality Initiative (ADQI) Workgroup focused on COVID-19–associated AKI recognized the need for data on anticoagulation and renal outcomes [7]. In this secondary analysis of a large, international, multiplatform, randomized clinical trial [6], we investigated whether therapeutic-dose heparin reduces the incidence of severe AKI or death in noncritically ill patients hospitalized for COVID-19.

2 | METHODS

Adults aged ≥18 years who were hospitalized for COVID-19 without the need for ICU-level care and expected to require hospitalization for ≥72 hours were enrolled in an open-label, randomized trial of therapeutic-dose heparin vs usual-care pharmacologic thromboprophylaxis [6]. Participants enrolled into the multiplatform randomized trial via the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) and A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19 (ACTIV-4a) platforms were included in this prespecified secondary analysis. Participants were

TABLE 1 Baseline characteristics.

	Overall (*n* = 1899)	Therapeutic-dose heparin (*n* = 1013)	Usual-care thromboprophylaxis (*n* = 886)
Age in years—mean (SD)	58.9 (14.1)	59.4 (14.1)	58.4 (14.1)
Male sex—*n* (%)	1109/1899 (58.4%)	607/786 (59.9%)	502/908 (56.7%)
Race group—*n* (%)			
Aboriginal/First Nations	18/1899 (0.9%)	11/1013 (1.1%)	7/886 (0.8%)
American Indian or Alaska Native	160/1899 (8.4%)	92/1013 (9.1%)	68/886 (7.7%)
Asian	74/1899 (3.9%)	37/1013 (3.7%)	37/886 (4.2%)
Black	326/1899 (17.2%)	187/1013 (18.5%)	139/886 (15.7%)
Native Hawaiian or Pacific Islander	6/1899 (0.3%)	2/1013 (0.2%)	4/886 (0.5%)
White	1064/1899 (56%)	554/1013 (54.7%)	510/886 (57.6%)
Other	84/1899 (4.4%)	46/1013 (4.5%)	38/886 (4.3%)
Unknown	167/1899 (8.8%)	84/1013 (8.3%)	83/886 (9.4%)
Hispanic or Latino	846/1845 (45.9%)	445/980 (45.4%)	401/865 (46.4%)
Body mass index (*n* = 1666)—median (IQR)[a]	29.9 (26.5, 34.6)	29.7 (26.3, 34.6)	30.1 (26.7, 34.7)
Pre-existing conditions—*n* (%)			
Hypertension	962/1816 (52.9%)	527/967 (54.5%)	435/849 (51.2%)
Diabetes mellitus, type 1 or 2	559/1849 (30.3%)	298/990 (30.1%)	261/856 (30.5%)
Prior myocardial infarction	21/1790 (1.2%)	9/959 (0.9%)	12/831 (1.4%)
Heart failure	84/1789 (4.7%)	44/958 (4.6%)	40/831 (4.8%)
Coronary artery disease	113/1795 (6.3%)	55/961 (5.7%)	58/834 (7.0%)
Peripheral artery disease	26/1794 (1.4%)	13/962 (1.4%)	13/832 (1.6%)
Cardiovascular disease	50/1788 (2.8%)	23/958 (2.4%)	27/830 (3.3%)
Chronic kidney disease[a]	116/1846 (6.3%)	63/990 (6.4%)	53/856 (6.2%)
Laboratory value—median (IQR)[b]			
Creatinine (baseline)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)
Estimated GFR[c]	83.3 (64.9, 103.1)	82.9 (63.9, 102.1)	84.2 (65.3, 104.1)
D-dimer—*n* (%)[d]			
<2× ULN	987/1569 (62.9%)	523/837 (62.5%)	464/732 (63.4%)
≥2× ULN	582/1569 (37.1%)	314/837 (37.5%)	268/732 (36.6%)
Therapies			
Glucocorticoid	1145/1847 (62%)	606/990 (61.2%)	539/857 (62.9%)
Remdesivir	704/1847 (38.1%)	375/990 (37.9%)	329/857 (38.4%)
Country of enrollment			
Brazil	440/1899 (23.2%)	233/1013 (23.0%)	207/886 (23.4%)
Canada	181/1899 (9.5%)	98/1013 (9.7%)	83/886 (9.4%)
Mexico	147/1899 (7.7%)	85/1013 (8.4%)	62/886 (7.0%)
Spain	128/1899 (6.7%)	64/1013 (6.3%)	64/886 (7.2%)
USA	1003/1899 (52.8%)	533/1013 (52.6%)	470/886 (53.0%)

(Continues)

TABLE 1 (Continued)

	Overall (*n* = 1899)	Therapeutic-dose heparin (*n* = 1013)	Usual-care thromboprophylaxis (*n* = 886)
Platform of enrollment			
ACTIV4	761/1899 (40.1%)	378/1013 (37.3%)	383/886 (43.2%)
ATTACC	1138/1899 (59.9%)	635/1013 (62.7%)	503/886 (56.8%)

ACTIV-4a, A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19; ATTACC, Antithrombotic Therapy to Ameliorate Complications of COVID-19; eGFR, estimated glomerular filtration rate.
[a]As defined by clinical history.
[b]IQR: 25th, 75th percentile.
[c]eGFR was determined according to the 2021 Chronic Kidney Disease Epidemiology Collaboration equations [9].
[d]D-dimer values were not measured in the remaining participants.

excluded if they had end stage kidney disease (ESKD) requiring dialysis at the time of trial enrollment. Participants enrolled into the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) platform were not included, since data on serum creatinine [SCr] were not available.

Participants assigned to therapeutic-dose heparin were dosed according to local hospital protocols for the treatment of acute venous thromboembolism for up to 14 days or until hospital discharge or recovery. Pharmacologic thromboprophylaxis was administered according to local clinical practice. Laboratory data, including serial measures of renal function, were assessed at baseline prior to randomization and at prespecified time points on days 1, 3, 5, 7, 10, 14, 21, and 28 following randomization.

The primary endpoint of this secondary analysis was in-hospital diagnosis of severe AKI or death. Severe AKI was defined according to stage 2 or 3 of the Kidney Disease: Improving Global Outcomes [KDIGO] criteria (≥2-fold increase in SCr from prerandomization baseline or initiation of kidney replacement therapy [KRT]). Secondary endpoints included stage 3 AKI or death, and KRT or death. Mortality was included in all key endpoints to account for the impact of death as a competing risk for AKI. Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis and was adjudicated in a blinded fashion by a clinical endpoint committee [8].

Bayesian hierarchical models with weakly informative priors estimated the risk of each outcome in those randomized to therapeutic-dose heparin vs usual-care pharmacologic thromboprophylaxis, adjusted for age, sex, baseline D-dimer concentration, enrollment period, country, enrollment site, and randomization platform, similar to the parent study statistical plan [6]. Models estimated the posterior probability of superiority for therapeutic-dose heparin, defined as a relative risk <1.0. A sensitivity analysis assessed associations between the heparin dosing strategy and the composite clinical endpoints among participants without baseline chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of ≥60 mL/min/1.73 m^2 [9]. To address death as a competing risk for AKI, an exploratory analysis was performed in which patients who died were assumed to have been free of AKI. The trial was approved by the relevant ethics committees and all participants, or their surrogates, provided written or oral informed consent.

3 | RESULTS AND DISCUSSION

Among 1922 ACTIV4a and ATTACC participants enrolled between April 2020 and January 2021, 23 with ESKD on dialysis at enrollment were excluded (Supplementary Figure). The mean age was 59 years, 58% were men, and the median baseline creatinine was 0.9 mg/dL. Detailed clinical characteristics of participants are shown in Table 1. Characteristics of patients with and without SCr measurements sufficient to diagnose AKI are shown in Supplementary Table.

Determination of AKI during hospitalization was not possible for 205 individuals without baseline or follow-up SCr measurements. Among the remaining 1694 participants, the primary endpoint of severe AKI or death occurred in 83 participants (4.9%), including 40/908 (4.4%) assigned to therapeutic-dose heparin and 43/786 (5.5%) assigned to usual-care pharmacologic thromboprophylaxis (adjusted relative risk [aRR]: 0.72; 95% credible interval [CrI]: 0.47, 1.10; posterior probability of superiority: 93.6%; Table 2, Figure). A total of 31 major bleeding events occurred in-hospital, with 24 events (2.4%) in participants assigned to therapeutic-dose heparin and 7 events (0.8%) in those assigned to usual-care pharmacologic thromboprophylaxis. There were fewer stage 2 or 3 AKI events (3.4% vs 3.9%) and deaths without stage 2 or 3 AKI (1.0% vs 1.5%) in the group assigned to therapeutic-dose heparin. Therapeutic-dose heparin was associated with a 97.7% probability of superiority to reduce the composite endpoint of stage 3 AKI or death (3.1% vs 4.6%; aRR: 0.64; 95% CI: 0.40, 0.99) compared to usual-care. In sensitivity analyses of participants without baseline CKD defined by an eGFR of ≥60 mL/min/1.73m^2 (*n* = 1596), therapeutic-dose heparin was associated with similarly strong reductions in the endpoints (Table 2). In an exploratory analysis in which patients who died were assumed free of AKI, therapeutic-dose heparin was associated with a 71% probability of superiority for stage 2 or 3 AKI (aRR: 0.88; CrI: 0.56, 1.38), an 80% probability of superiority for stage 3 AKI (aRR: 0.75; CrI: 0.38, 1.46), and a 72% probability of superiority for KRT (aRR: 0.76; CrI: 0.29, 1.94).

AKI is a relatively common complication of COVID-19. Among patients hospitalized for COVID-19 early in the pandemic, prior to the introduction of disease-modifying therapies or effective vaccines, the incidence of AKI was reported to be as high as 30% to 50% [1-4,10]. In a cohort study of 3993 patients hospitalized for COVID-19 at

TABLE 2 Associations between therapeutic-dose heparin use and AKI outcomes.

	Therapeutic-dose heparin *N* = 908	Usual-care thromboprophylaxis *N* = 786	Unadjusted RR (95% CrI)	Adjusted RR (95% CrI)[a]	Probability of superiority, %
Overall cohort					
AKI stage 2 or 3 or death	40 (4.4%)	43 (5.5%)	0.81 (0.52, 1.24)	0.72 (0.47, 1.10)	93.6
AKI stage 2 or 3[b]	31 (3.4%)	31 (3.9%)			
Death in hospital	15 (1.7%)	21 (2.7%)			
Death in hospital without AKI	9 (1.0%)	12 (1.5%)			
AKI stage 3 or death	28 (3.1%)	36 (4.6%)	0.67 (0.41, 1.10)	0.64 (0.40, 0.99)	97.7
KRT or death	21 (2.3%)	30 (3.8%)	0.66 (0.34, 1.10)	0.63 (0.37, 0.99)	97.7
Participants without baseline CKD[c]	*N* = 861	*N* = 735			
AKI stage 2 or 3 or death	33 (3.8%)	35 (4.8%)	0.84 (0.50, 1.30)	0.86 (0.53, 1.31)	78.2
AKI stage 3 or death	22 (2.6%)	28 (3.8%)	0.71 (0.38, 1.19)	0.70 (0.39, 1.16)	92.0
KRT or death	16 (1.9%)	25 (3.4%)	0.59 (0.29, 1.05)	0.55 (0.27, 1.00)	97.6

AKI, acute kidney injury; CKD, chronic kidney disease; CrI, credible interval; KRT, kidney replacement therapy.
[a]95% CrI; adjusted for age, sex, D-dimer, enrollment period, country, site, and trial platform.
[b]Three individuals did not have complete information to define AKI but died in hospital.
[c]estimated glomerular filtration rate ≥60, as calculated by the CKD-EPI equation.

a large urban health care system, 46% developed AKI, with KDIGO stages 2 and 3 reported in 19% and 42% of cases, respectively [3]. COVID-19–associated AKI is independently associated with high in-hospital all-cause mortality [1,3].

The pathophysiology of AKI in COVID-19 is complex and is thought to involve immune responses to viral infection, inflammation, endothelial injury, coagulopathy, and microvascular thrombosis [4,11,12]. Although acute tubular injury is the most common finding at autopsy in patients with COVID-19–associated AKI, platelet-rich peritubular fibrin microthrombi are reported in the renal microcirculation [12]. Therapeutic-dose heparin may inhibit acute inflammation [5] and mitigate microvascular thrombosis, thereby preventing or attenuating AKI.

In the current analysis of noncritically ill adults hospitalized for COVID-19, fewer patients developed stage 2 or 3 AKI than reported

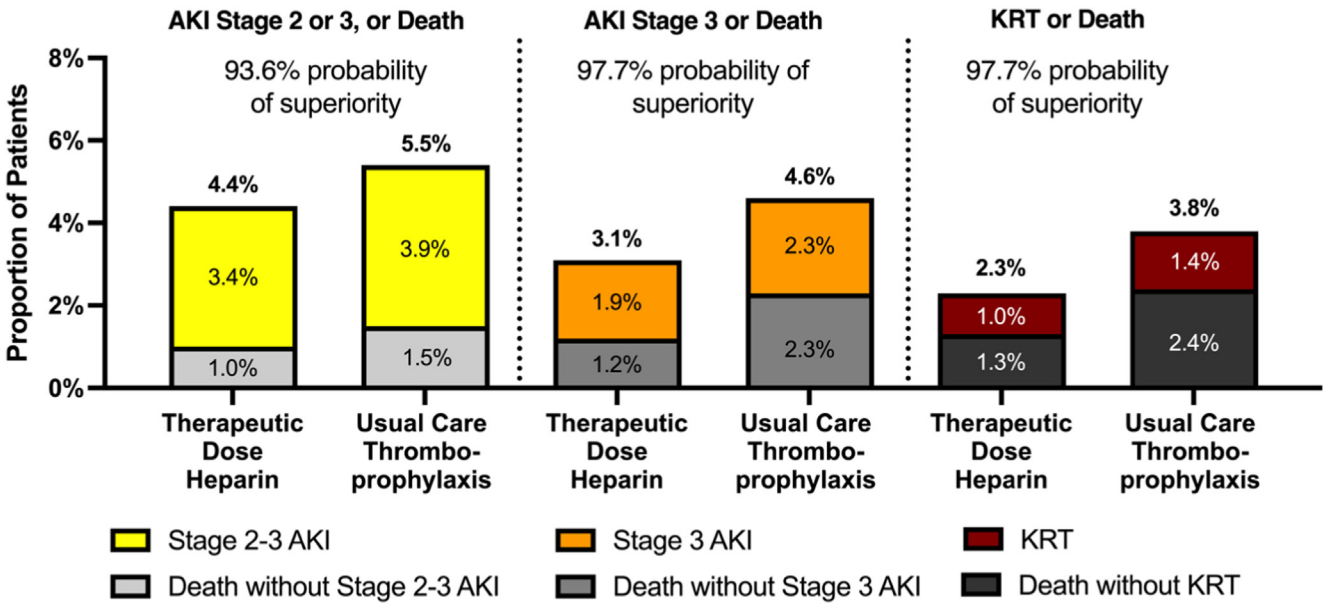

FIGURE AKI outcomes by randomized assignment to therapeutic-dose heparin vs usual-care pharmacologic thromboprophylaxis. *Unadjusted proportions and Bayesian hierarchical model estimates of the posterior probability of superiority for therapeutic-dose heparin (adjusted for age, sex, D-dimer, enrollment period, country, site, and trial platform) are shown. AKI, acute kidney injury; KRT, kidney replacement therapy.

in prior series. Still, therapeutic-dose heparin was associated with a 97% probability of superiority to reduce in-hospital stage 3 AKI or death, and a 94% probability of superiority to reduce stage 2 or 3 AKI and death. The composite outcomes were driven by both numerically fewer episodes of AKI and in-hospital death. Findings were directionally consistent in exploratory analyses when death was not a competing risk for AKI (eg, patients who died were assumed free of AKI). These findings suggest that, in addition to reduced use of cardiovascular or respiratory organ support and lower mortality, therapeutic-dose heparin may reduce risks of AKI in COVID-19; this finding should be integrated into risk and benefit considerations for treatment of noncritically ill patients hospitalized for COVID-19 [6].

This was a prespecified secondary analysis of a large, open-label, multiplatform clinical trial with some limitations. Laboratory measurements were recorded only at prespecified time points after randomization, and fluctuations in SCr may have been missed by intermittent sampling, potentially underestimating the incidence or severity of AKI. A composite endpoint was selected rather than AKI alone due to competing risks of death. Baseline or follow-up SCr values were missing in nearly 11% of the eligible cohort, although differences in baseline characteristics were minor. Participants were enrolled early in the pandemic when wild-type and alpha strains causing COVID-19 were prevalent, and prior to widespread vaccination for COVID-19, vaccine boosters, less virulent Omicron COVID-19 variants, and the US approval of ritonavir-boosted nirmatrelvir for acute COVID-19 [13]. Thus, subsequent advances in therapy for COVID-19 may affect risk–benefit considerations for the use of therapeutic-dose heparin to reduce AKI and mortality in the current era.

4 | CONCLUSIONS

In this analysis of a randomized trial, therapeutic-dose heparin was associated with a high probability of superiority to reduce the incidence of in-hospital severe AKI or death in noncritically ill adults hospitalized for COVID-19 compared with usual-care pharmacologic thromboprophylaxis.

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AUTHOR CONTRIBUTIONS

N.R.S., E.M.H., M.D.N., and J.S.B. are responsible for study conception, design, and data and statistical analysis and wrote the manuscript. L.K., L.A.C., M.C., M.F., M.N.G., K.S.K., H.R.R., R.Z., and J.S.H. contributed to the study design and data analysis and provided key revisions to the manuscript. A.H., B.J.H., A.K., P.L., D.E.L., E.G., E.S.L., and B.J.M. contributed to study design and data analysis, and reviewed and edited the manuscript.

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DATA AVAILABILITY

De-identified participant data will be shared through BioCatalyst.

RELATIONSHIP DISCLOSURE

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TWITTER

Nathaniel R. Smilowitz @NSmilowitzMD
Erinn M. Hade @hade_em
Jeffrey S. Berger @plateletdoc

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SUPPLEMENTARY MATERIAL

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