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ORIGINAL ARTICLE

High-risk subgroups were not identified to benefit from thromboprophylaxis after hospitalization for COVID-19

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Abstract

Background: The Accelerating COVID-19 Therapeutic Interventions and Vaccines-4c (ACTIV-4c) trial investigated prophylactic apixaban for 30 days following hospitalization for COVID-19. The overall incidence of early postdischarge death or thromboembolism was low, and the trial was closed early.

Objectives: To identify a high-risk patient population who might benefit from postdischarge thromboprophylaxis through subgroup analyses stratified by age, race/ethnicity, obesity, D-dimer elevation, World Health Organization score, and modified International Medical Prevention Registry on Venous Thromboembolism score on 30-day composite outcome of all-cause death, arterial thromboembolism (ATE), and venous thromboembolism (VTE).

Methods: Cumulative incidences of all-cause death, ATE, and VTE within 30 days were described for each subgroup. Time to death, ATE, or VTE by 30 days was analyzed using Cox proportional hazard models with interaction testing for each subgroup.

Results: Among 1217 patients randomized to apixaban or placebo group, 32% were >60 years old. Modified International Medical Prevention Registry on Venous Thromboembolism score was ≥4 in 2% and 2 or 3 with an elevated D-dimer in an additional 9% of participants. The overall incidence of the primary endpoint was 2.13% in the apixaban group and 2.31% in the placebo group. At day 30, similar rates of the primary endpoint occurred within subgroups, except for participants aged >60 years. No benefit of thromboprophylaxis was seen in any subgroup.

Conclusion: The combined incidence of 30-day death, ATE, and VTE was low in patients who survived COVID-19 hospitalization, except in patients over age 60 years. Due to the limited number of events, the findings remain inconclusive; nonetheless, the study did not identify a high-risk subgroup that would derive benefits from extended thromboprophylaxis.

This study was presented as an abstract at the International Society on Thrombosis and Haemostasis Congress, 2023.

KEYWORDS
anticoagulants, COVID-19, hospitalization, patient discharge, venous thromboembolism

Essentials

- Incidence of postdischarge death or venous thromboembolism was low in Accelerating COVID-19 Therapeutic Interventions and Vaccines-4c (ACTIV-4c) trial.
- We aimed to identify a high-risk patient population through subgroup analysis.
- There was a low incidence of death, arterial thromboembolism, and venous thromboembolism, except in patients over age 60.
- Age, COVID-19 severity, D-dimer, and risk scores did not predict benefit from thromboprophylaxis.

1 | INTRODUCTION

Hospitalized patients with SARS-CoV-2 are at an increased risk for thrombotic events, which contribute to overall morbidity and mortality [1,2]. Early in the pandemic, high incidence of death and thrombotic complications occurred after hospital discharge [3–5]. Prior to COVID-19, randomized trials including the Medically Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolism Risk (MARINER) and Acute Medically Ill Venous Thromboembolism (VTE) Prevention with Extended Duration Betrixaban (APEX) trials showed that anticoagulant therapy could reduce venous thromboembolism (VTE) risk in select, high-risk patients with a recent hospitalization for an acute medical illness [6–8]. The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-4c trial was designed to evaluate whether postdischarge anticoagulant therapy benefited all hospitalized patients with COVID-19.

The ACTIV-4c trial randomized 1217 patients who were hospitalized for symptomatic COVID-19 for >48 hours to receive apixaban 2.5 mg orally twice daily or placebo for 30 days after hospital discharge [9]. The 30-day composite primary endpoint of all-cause mortality, VTE, or arterial thromboembolism (ATE) occurred in 2.1% of patients treated with apixaban compared with that in 2.3% of patients who received placebo. Infrequent major bleeding events occurred (apixaban arm 0.4% vs placebo arm 0.2%). Clinically relevant nonmajor bleeding occurred in 0.6% of people taking apixaban and 1.1% of those receiving placebo. The ACTIV-4c trial was stopped early because of low observed 30-day postdischarge death/VTE/ATE rates. We aimed to evaluate whether a high-risk subgroup could be identified that would potentially benefit from extended thromboprophylaxis after hospital discharge.

2 | METHODS

ACTIV-4c was a prospective, randomized, double-blind, placebo-controlled trial that assigned the participants discharged from hospitals to either 2.5 mg of apixaban twice daily or matching placebo to investigate the effectiveness of thromboprophylaxis to reduce the primary endpoint of all-cause death, VTE, or ATE within 30 days of randomization. The study population included participants aged older than 18 years who were admitted to hospitals for SARS-CoV-2 infection for at least 48 hours, with the randomized treatment starting the day after hospital discharge. The prespecified variables of interest were age (≤60 years vs >60 years), race (White vs Black vs other races), ethnicity (Hispanic vs non-Hispanic), body mass index (<25, 25-30, ≥30 kg/m^2), sex (male vs female), D-dimer within 72 hours before discharge (normal vs >upper limit of normal), length of hospital stay (<7 vs ≥7 days), World Health Organization (WHO) COVID-19 severity score (<5 vs ≥5), and the modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE VTE) risk score (IMPROVE VTE score of <2 or a score of 2 or 3 with normal D-dimer vs IMPROVE VTE score of ≥4 or a score of 2 or 3 with elevated D-dimer) [10]. The IMPROVE VTE score is a risk assessment model of points for risk factors including previous VTE (3 points), thrombophilia (2 points), lower limb paralysis (2 points), active cancer (2 points), immobilization (1 point), intensive care unit (ICU) stay (1 point), and age > 60 years (1 point) [10]. In the original cohort of hospitalized medically ill patients, people with a score of ≥4 had a 5.7% incidence of VTE at 3 months compared with 1.5% incidence in people with score of 2 or 3 [11].

Baseline characteristics of the patients were summarized by randomly assigned treatment groups with frequencies for categorical variables and using means and SDs for continuous variables. Our primary hypothesis was that the treatment effect of apixaban on time to all-cause death, ATE, or VTE at 30 days would differ by patient characteristics. Time-to-first event among all-cause death, VTE, or ATE within 30 days was compared between the 2 treatment groups for each subgroup using Kaplan–Meier curves and log-rank tests. Cox proportional hazard models were used for each subgroup to analyze time to death, VTE, or ATE within 30 days. We presented estimated hazard ratios and the associated 95% CIs. The *P* value threshold for statistical significance for all analyses was set to be .05.

The 30-day event rates within subgroups were also presented with the number of events for the 2 treatment groups. Two-sided *Z* test for proportions was conducted for comparing the 30-day event rates for subgroups (eg, ≤60 years vs >60 years). The exact 95% CIs were computed for the event rates in each subgroup, whereas for the difference in event rates between 2 groups, asymptotic 95% CI was used.

Locally estimated scatterplot smoothing curve was used to graphically assess the association between the 30-day event

occurrence and continuous variables such as age in the study population as well as in each treatment group.

The risk of the 30-day events was predicted using a log-binomial regression model, including all the subgroup variables. The participants were then stratified into 3 groups using the first quantile of predicted risk (0.877%) and third quantile of predicted risk (3.372%). The heterogeneity of treatment effects based on the risk is reported in the Supplementary Table. All analyses were performed using SAS version 9.4 (SAS Institute) and R version 4.3.1.

3 | RESULTS

In the ACTIV-4c trial, 1217 patients were randomized to apixaban or placebo for 30 days after hospital discharge for COVID-19. Participants were recruited between February 2021 and June 2022, which correspond to the Beta through Omicron variant waves. Recruitment by COVID-19 wave included 15% prior to the Delta variant, ~50% during the Delta variant, 20% between Delta and Omicron variants, and 15% during the Omicron variant [9]. Given the timing of the trial, 32% of participants had received the first dose of vaccine, 21% had received 2 doses, and 6.6% had received 3 doses of vaccine. Treatment for COVID-19 included dexamethasone (86.1%), remdesivir (72.6%), other steroids (15.5%), and convalescent plasma (3.7%). Overall, 32.1% of participants were aged >60 years. Breakdown of participants by ethnicity was similar to the US population, with 16.7% self-identified as Hispanic compared with 18.7% in the US Census identifying as Hispanic or Latino [12]. A higher proportion of people self-identified as Black in the ACTIV-4c trial (26.5%) compared with the US population (12.1%) [12]. A majority of participants were obese, with 63.9% of participants having a body mass index of ≥30 kg/m^2. D-dimer evaluated within 72 hours prior to hospital discharge was elevated in 56.3% of participants. The WHO severity score was ≥5 (required high-flow oxygen or more significant levels of support) in 30.7% of participants. Thirteen percent of people required treatment in an ICU during their hospitalization. The modified IMPROVE VTE score was ≥4 in 2.1% and was 2 or 3 with an elevated D-dimer in an additional 8.2% of participants. Individual characteristics distributed according to whether the participants received placebo or apixaban are shown in the Table.

The overall incidence of the primary endpoint was 2.1% in the apixaban group and 2.3% in the placebo group. Subgroups were evaluated by demographic variables, D-dimer within 72 hours of discharge, length of stay in the hospital, and the IMPROVE VTE score. At day 30, similar rates of the primary endpoint occurred within subgroups based on race, sex, length of stay of <7 vs ≥7 days, and WHO severity score of <5 vs ≥5 (Figure 1). The largest differences in outcomes were by age as 1.1% (exact 95% CI, 0.5%-2.1%) of participants aged ≤60 years experienced the primary outcome compared with 4.6% (95% CI, 2.8%-7.2%) of participants aged >60 years (Figure 1), leading to an estimated difference of 3.5% (95% CI, 1.3%-

TABLE Demographics of the Accelerating COVID-19 Therapeutic Interventions and Vaccines-4c trial participants.

Demographic	Placebo (*N* = 607)	Apixaban (*N* = 610)
Age (y)		
≤60	418 (68.9)	408 (66.9)
>60	189 (31.1)	202 (33.1)
≥75	19 (3.1)	30 (4.9)
Age (y), mean (SD)	52.4 (13.2)	52.8 (14.3)
Race		
White	363 (59.8)	350 (57.4)
Black or African American	154 (25.4)	168 (27.5)
Asian	12 (2.0)	10 (1.6)
American Indian or Alaska Native	4 (0.7)	6 (1.0)
Native Hawaiian or other Pacific Islander	5 (0.8)	2 (0.3)
More than 1 race	3 (0.5)	5 (0.8)
Other race	20 (3.3)	24 (4.0)
Unknown	46 (7.6)	45 (7.4)
Hispanic or Latin ethnicity	103 (17.0)	100 (16.4)
BMI (kg/m^2)		
<25	81 (13.3)	80 (13.1)
25-30	125 (20.6)	133 (21.8)
≥30	391 (64.4)	387 (63.4)
Sex		
Female	303 (49.9)	311 (51.0)
Male	304 (50.1)	299 (49.0)
Maximal WHO severity score ≥5	185 (30.5)	189 (31.0)
D-dimer within 72 h of discharge		
Normal	249/601 (41.4)	276/600 (46.0)
>ULN	352/601 (58.6)	324/600 (54.0)
>2-fold ULN	139/601 (23.1)	129/600 (21.5)
>4-fold ULN	58/601 (9.7)	44/600 (7.33)
IMPROVE VTE Risk Score factor (VTE Risk Score)		
Previous VTE (3)	9 (1.5)	9 (1.5)
Known thrombophilia (2)	1 (0.2)	0 (0)
Current lower limb paralysis or paresis (2)	0 (0)	2 (0.3)
History of cancer (2)	35 (5.8)	36 (5.9)
ICU/CCU stay (1)	82 (13.5)	82 (13.4)

(Continues)

TABLE (Continued)

Demographic	Placebo (*N* = 607)	Apixaban (*N* = 610)
Complete immobilization ≥1 d (1)	84 (13.8)	94 (15.4)
Age ≥ 60 y (1)	189 (31.1)	202 (33.1)
IMPROVE VTE Risk Score ≥4	12 (2.0)	14 (2.3)
IMPROVE VTE Risk Score 2-3 with D-dimer >ULN	49 (8.1)	51 (8.4)

Values are *n* (%) for categorical variables and mean (SD) for numeric variables.

BMI, body mass index; CCU, critical care unit; ICU, intensive care unit; IMPROVE VTE, International Medical Prevention Registry on Venous Thromboembolism; ULN, upper limit of normal; VTE, venous thromboembolism; WHO, World Health Organization.

5.7%). The incidence of the primary outcome in participants with an IMPROVE VTE score of ≥4 or 2 or 3 with an elevated D-dimer was 3.2% compared with 2.1% in the lower IMPROVE VTE score group (Figure 1).

We then evaluated if apixaban showed benefit by each subgroup (Figure 2). A trend toward a lower frequency of the composite outcome of death, ATE, and VTE was suggested in participants with WHO severity score of ≥5 and participants aged ≤60 years, but the differences were not statistically significant. Overall, we did not observe a significant benefit of extended thromboprophylaxis for any of the subgroups.

The primary endpoint was then regressed on continuous age using locally estimated scatterplot smoothing method in the overall study population, and from age of ≥60 years, there was an increasing trend in the likelihood of the combined event of VTE, ATE, or death at 30 days (Figure 3). However, when we evaluated it by treatment groups, the likelihood of combined event at 30 days overlapped over most age ranges (Figure 4). The sharp increase in the event rate for higher age range was due to 1 event in the extreme age group after censoring at age of 85 years.

The overall result from the heterogeneity of treatment effects had 8% relative risk reduction, suggesting that apixaban reduced the risk of the composite outcome of death, ATE, and VTE by 8% compared with the placebo group (Supplementary Table). It was consistent with the results of predicted risk of <0.877% and predicted risk between 0.877% and 3.37% as benefit was present in the apixaban group. However, in predicted risk of >3.372%, more patients in the apixaban group had events than those in the placebo group, but the difference was not statistically significant. Overall, the 95% CIs showed that the results were not statistically significant.

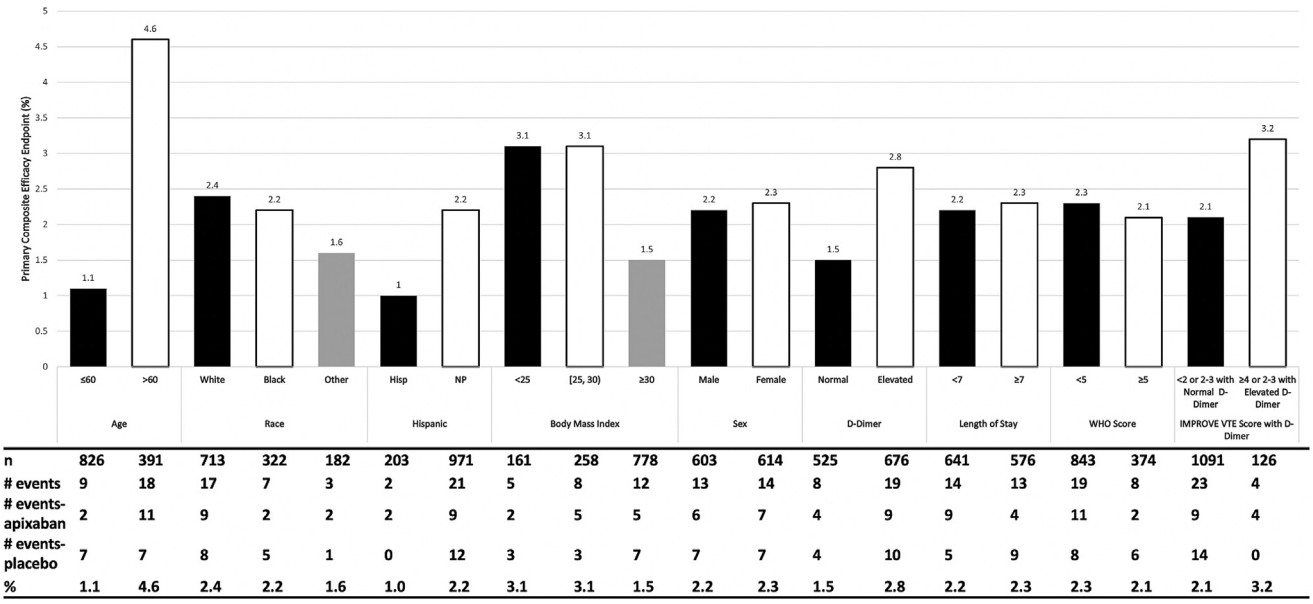
4 | DISCUSSION

The ACTIV-4c trial showed that there was a low overall incidence of the composite outcome of VTE, ATE, or death at 30 days in adults hospitalized for ≥48 hours for COVID-19 in the United States. The incidence of VTE, ATE, or death at 30 days within each subgroup was similar, with the exception of participants aged >60 years compared with participants aged ≤60 years. Due to the limited number of events, the findings remain inconclusive; nonetheless, the subgroup analysis did not identify any subset of patients hospitalized with COVID-19 that would benefit from extended thromboprophylaxis after hospital discharge, including patients aged >60 years.

The findings from the ACTIV-4c trial contrast with the findings from the Medically Ill hospitalized Patients for COVID-19 THrombosis Extended ProphyLaxis with rivaroxaban ThErapy (MICHELLE) trial, an open-label study of 320 patients randomized to rivaroxaban 10 mg daily for 35 days or standard of care [13]. To be eligible for the MICHELLE trial, participants either needed an IMPROVE VTE score of ≥4 or a score of 2 or 3 with an elevated D-dimer. The MICHELLE trial used the highest D-dimer during the hospitalization, whereas the ACTIV-4c trial used the D-dimer result within 72 hours of hospital discharge. MICHELLE was completed during the Alpha-Gamma waves in Brazil compared with the Beta-Omicron waves in the United States studied in ACTIV-4c. Demographics differed between the studies, with 4% of participants aged 75 years or older in ACTIV-4c compared with 10% of participants in MICHELLE. Additionally, 52% of participants in MICHELLE required hospitalization in an ICU compared with 13% in the ACTIV-4c study, potentially due to differences in illness severity, changes in hospital capacity, or experience in managing COVID-19. Of note, hospitalization in the ICU is a part of the IMPROVE VTE score, upon which the MICHELLE study based its enrollment. Vaccination, which affects illness severity, also differed as 32% of ACTIV-4c participants had received 1 dose of vaccine, whereas vaccines were approved in Brazil only 4 months prior to completing enrollment in the MICHELLE study [13,14]. The MICHELLE study used screening ultrasounds and computed tomography scans to identify asymptomatic VTE events and showed lower rates of death and symptomatic VTE in patients treated with rivaroxaban. The event rates that occurred in the standard of care arm of MICHELLE were significantly higher than those seen in ACTIV-4c, even in patients meeting the same inclusion criteria. Differences in severity of illness, treatment during the hospitalization, and patient population may account for the discordant results between the MICHELLE and ACTIV-4c trials.

The ACTIV-4c trial results are similar to incidence of thrombosis seen in similar patient cohorts. Several meta-analyses have summarized postdischarge arterial and venous thrombosis over the course of the pandemic [15–17]. The first meta-analysis of 11 studies showed a cumulative postdischarge pooled incidence of VTE of 1.8% [15]. A subsequent meta-analysis of 16 studies found a 1.16% incidence of VTE and 1.45% incidence of arterial events after discharge from COVID-19 hospitalization [16]. Heterogeneity between trial outcomes occurred, which limits the ability to compare across studies.

The ACTIV-4c trial had several limitations, which also influenced the subgroup analysis. The overall event rates were lower than original projections due to overestimation of the outcome and changing course of the disease over time. The incidence of VTE and ATE was 22- and 33-fold higher, respectively, in the week after COVID-19



n	826	391	713	322	182	203	971	161	258	778	603	614	525	676	641	576	843	374	1091	126
# events	9	18	17	7	3	2	21	5	8	12	13	14	8	19	14	13	19	8	23	4
# events-apixaban	2	11	9	2	2	2	9	2	5	5	6	7	4	9	9	4	11	2	9	4
# events-placebo	7	7	8	5	1	0	12	3	3	7	7	7	4	10	5	9	8	6	14	0
%	1.1	4.6	2.4	2.2	1.6	1.0	2.2	3.1	3.1	1.5	2.2	2.3	1.5	2.8	2.2	2.3	2.3	2.1	2.1	3.2

FIGURE 1 Incidence of venous thromboembolism (VTE), arterial thromboembolism, or death at 30 days within subgroups. Hisp, Hispanic; IMPROVE VTE, International Medical Prevention Registry on VTE; NP, non-Hispanic.

diagnosis in 2020 [18]. However, studies have shown a decrease in incidence of thrombosis with subsequent COVID variants, which may be attributable to use of dexamethasone and antiviral therapy, decreased severity of illness after vaccination, or differences in coagulation system activation by viral variants [19,20]. Differences in incidence of events have also been found in different countries [21]. ACTIV-4c was conducted in the United States; thus, estimates of thrombosis from other areas may not have applied. With the introduction of COVID-19 vaccination, hospitalization rates decreased significantly, leading to fewer eligible patients [22]. Additionally, the

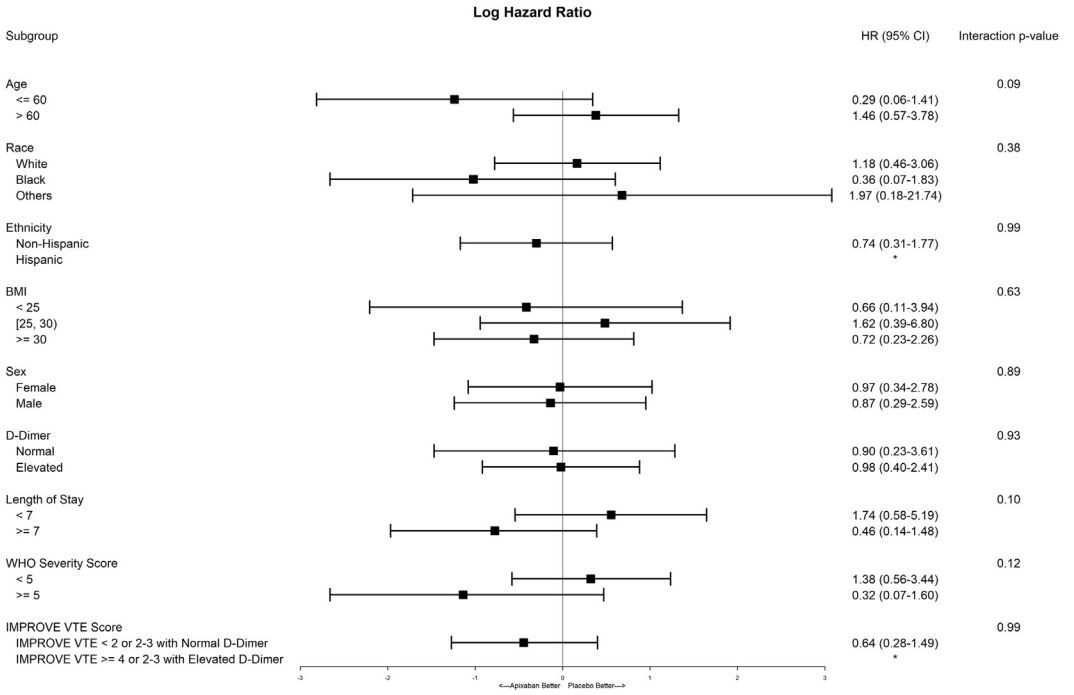


FIGURE 2 Time to all-cause death, arterial thromboembolism, or venous thromboembolism (VTE) at 30 days using Cox proportional hazard models. Hazard ratio (HR) and 95% CIs for apixaban vs placebo in various subgroups. *In the International Medical Prevention Registry on VTE (IMPROVE VTE) score of ≥4 or 2 or 3 with an elevated D-dimer subgroup, there were no events in participants receiving placebo (n = 61) compared with 4 events in the apixaban group (n = 65). There were no events in participants receiving placebo (n = 103) compared with 2 events in the apixaban group (n = 100). Therefore, the HR for both subgroups could not be estimated. BMI, body mass index; WHO, World Health Organization.

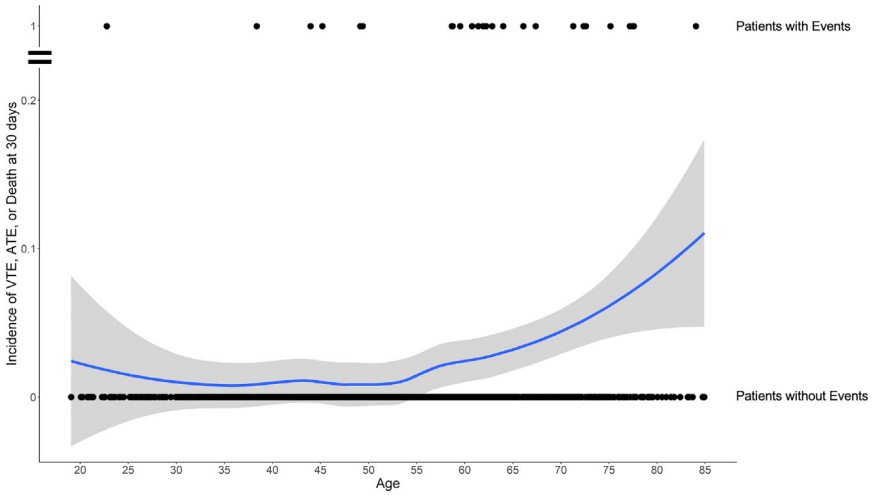


FIGURE 3 Locally estimated scatterplot smoothing curve between age and incidence of venous thromboembolism (VTE), arterial thromboembolism (ATE), or death at 30 days. Participants without events are denoted with dots at the bottom of the figure. Participants with events are denoted by dots at the top of the figure. There were 4 patients older than 85 years old: 3 in the apixaban group and 1 in the placebo group. Only 2 patients in the apixaban group had a primary endpoint.

willingness to participate in research declined. All of these factors led to fewer events than expected and a decision to discontinue enrollment in the ACTIV-4c trial.

Overall, the incidence of VTE, ATE, or death in patients after hospitalization in the United States with COVID-19 is low. Because of the low number of events, the results are inconclusive, but a high-risk subgroup that would benefit from extended thromboprophylaxis was not identified.

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ETHICS STATEMENT

The work described has not been published previously (except as an abstract to the International Society on Thrombosis and Haemostasis Congress 2023), it is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder. The authors ensure that the work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

AUTHOR CONTRIBUTIONS

L.B.K., T.Y.W., and T.L.O. were involved in the concept and design, interpretation of data, writing, revising, and final approval of the

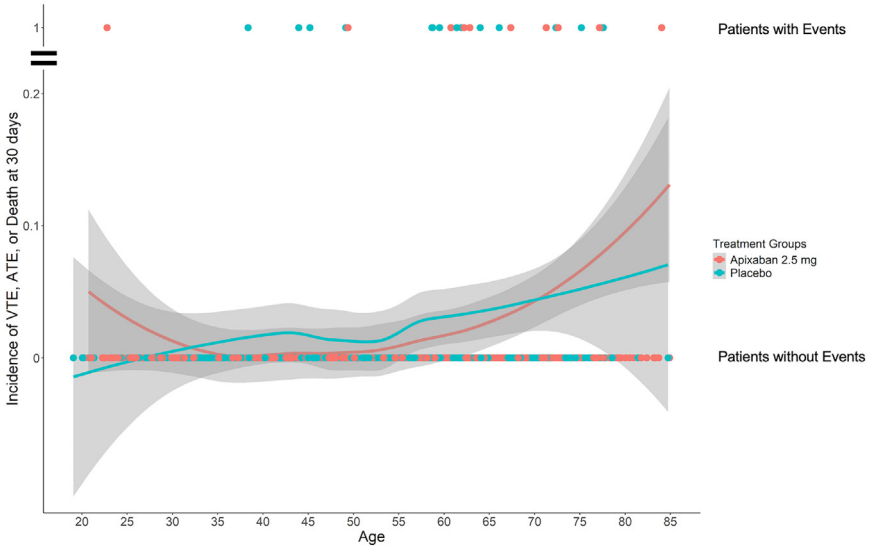

FIGURE 4 Locally estimated scatterplot smoothing curve between age and incidence of venous thromboembolism (VTE), arterial thromboembolism (ATE), or death at 30 days by treatment groups. Participants without events are denoted at bottom of the figure, with participants randomized to apixaban in orange and placebo in teal. Participants with events are denoted by dots at the top of the figure. There were 4 patients older than 85 years old: 3 in the apixaban group and 1 in the placebo group. Only 2 patients in the apixaban group had a primary endpoint.

manuscript. R.S.K., L.W., and P.J.M. were involved with data interpretation, revising, and approval of the manuscript. T.K. was involved with the concept and design, analysis and interpretation of data, writing and revising, and final approval of the manuscript. K.E., A.S.W., and K.J.A. were involved with the concept and design, analysis and interpretation of data, and revising and final approval of the manuscript.

RELATIONSHIP DISCLOSURE

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SUPPLEMENTARY MATERIAL

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