

ORIGINAL RESEARCH

# Eligibility for Posthospitalization Venous Thromboembolism Prophylaxis in Hospitalized Patients With COVID-19: A Retrospective Cohort Study

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**BACKGROUND:** A recent randomized trial, the MICHELLE trial, demonstrated improved posthospital outcomes with a 35-day course of prophylactic rivaroxaban for patients hospitalized with COVID-19 at high risk of venous thromboembolism. We explored how often these findings may apply to an unselected clinical population of patients hospitalized with COVID-19.

**METHODS AND RESULTS:** Using a 35-hospital retrospective cohort of patients hospitalized between March 7, 2020, and January 23, 2021, with COVID-19 (MI-COVID19 database), we quantified the percentage of hospitalized patients with COVID-19 who would be eligible for rivaroxaban at discharge per MICHELLE trial criteria and report clinical event rates. The main clinical outcome was derived from the MICHELLE trial and included a composite of symptomatic venous thromboembolism, pulmonary embolus-related death, nonhemorrhagic stroke, and cardiovascular death at 35 days. Multiple sensitivity analyses tested different eligibility and exclusion criteria definitions to determine the effect on eligibility for postdischarge anticoagulation prophylaxis. Of 2016 patients hospitalized with COVID-19 who survived to discharge and did not have another indication for anticoagulation, 25.9% (n=523) would be eligible for postdischarge thromboprophylaxis per the MICHELLE trial criteria (range, 2.9%–39.4% on sensitivity analysis). Of the 416 who had discharge anticoagulant data collected, only 13.2% (55/416) were actually prescribed a new anticoagulant at discharge. Of patients eligible for rivaroxaban per the MICHELLE trial, the composite clinical outcome occurred in 1.2% (6/519); similar outcome rates were 5.7% and 0.63% in the MICHELLE trial's control (no anticoagulation) and intervention (rivaroxaban) groups, respectively. Symptomatic venous thromboembolism events and all-cause mortality were 6.2% (32/519) and 5.66% in the MI-COVID19 and MICHELLE trial control cohorts, respectively.

**CONCLUSIONS:** Across 35 hospitals in Michigan, ≈1 in 4 patients hospitalized with COVID-19 would qualify for posthospital thromboprophylaxis. With only 13% of patients actually receiving postdischarge prophylaxis, there is a potential opportunity for improvement in care.

**Key Words:** anticoagulants ■ COVID-19 ■ patient discharge ■ rivaroxaban ■ venous thromboembolism

**H**ospitalization and COVID-19 infection are both key risk factors for venous thromboembolism (VTE). However, there are conflicting observational

data on the burden of posthospital VTE among patients hospitalized for COVID-19, with incidence ranging from 0.6% to 4.8% after discharge, depending on

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## CLINICAL PERSPECTIVE

### What Is New?

- In a cohort of 2016 patients hospitalized with COVID-19 across 35 hospitals who survived until discharge, 25.9% (n=523) would be eligible for postdischarge thromboprophylaxis per the MICHELLE trial criteria (range, 2.9%–39.4% on sensitivity analysis).
- Of the 416 who had discharge anticoagulant data collected, only 13.2% (55/416) were actually prescribed a new anticoagulant at discharge.

### What Are the Clinical Implications?

- Approximately 1 in 4 patients discharged after a hospital stay with COVID-19 would qualify for postdischarge thromboembolism prophylaxis per the MICHELLE trial criteria.
- Patients with COVID-19 should be screened for consideration of thromboembolism prophylaxis at hospital discharge.

## Nonstandard Abbreviations and Acronyms

<b>IMPROVE</b>	International Medical Prevention Registry on Venous Thromboembolism
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the population studied and follow-up time.<sup>1–5</sup> Multiple randomized clinical trials<sup>6–9</sup> have explored the role of extended thromboprophylaxis with low-dose, direct-acting oral anticoagulants (including rivaroxaban) in patients without COVID-19, with some showing a net benefit.

A recent randomized trial, the MICHELLE trial, showed an improvement in their composite 35-day outcome (ie, symptomatic or fatal VTE, asymptomatic VTE, symptomatic arterial thromboembolism [myocardial infarction, nonhemorrhagic stroke, and major adverse limb event], and cardiovascular death) and in a composite outcome of symptomatic VTE, myocardial infarction, stroke, and cardiovascular death in patients hospitalized with COVID-19 who were at high risk of VTE and discharged on prophylactic dosing of rivaroxaban (10 mg/d).<sup>10</sup> However, individual components of the MICHELLE trial's primary outcome (eg, symptomatic VTE) were no different. In addition, posthospital VTE rates from observational data sets have been highly variable (0.2%–14.8%),<sup>4,11,12</sup> and the practice of posthospital thromboprophylaxis had not been broadly adopted before the COVID-19 pandemic.<sup>13,14</sup> As with all clinical trials, it remains unclear how generalizable the

clinical trial population and results are to an unselected population of patients.

To help interpret how the MICHELLE trial results might apply to a broad clinical population, we used a 35-hospital retrospective database to identify how many patients with COVID-19 should potentially be prescribed rivaroxaban at discharge.

## METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols must be approved by the Data, Design, and Publications Committee for the MI-COVID19 database. Requests can be sent to the corresponding author at the University of Utah.

### MI-COVID19 Consortium

MI-COVID19 was a statewide collaborative quality initiative sponsored by Blue Cross Blue Shield of Michigan and Blue Care Network. MI-COVID19 was created in 2020 to improve the care of hospitalized patients with COVID-19 through data collection and sharing.<sup>15,16</sup> No standardized treatment protocols were provided as part of MI-COVID19. Institutional participation in MI-COVID19 was voluntary and arranged through a special collaboration of hospitals participating in other Blue Cross Blue Shield–sponsored collaborative quality initiatives; notably, one prior collaborative quality initiative (the Michigan Hospital Medicine Safety Consortium) was focused on reducing VTE in hospitalized medical patients, providing the collaborative with data collection experience and infrastructure.<sup>17,18</sup> Of the 92 non-critical access, nonfederal hospitals in Michigan, 45 (49%) were participating in Michigan Hospital Medicine Safety Consortium at the time of the first COVID-19 wave. Of those, 35 hospitals (78%) elected to participate in MI-COVID19. Michigan Hospital Medicine Safety Consortium hospitals that volunteered for MI-COVID19 were similar to those that elected not to participate (Table S1). MI-COVID19 hospitals have a median bed size of 317 (interquartile range, 191–443), are located throughout Michigan, and generally self-identify as nonprofit (83%).

### MI-COVID19 Patient Population and Sampling

Our primary cohort of interest was adults hospitalized for COVID-19 from March 7, 2020, to January 23, 2021. Patients were excluded if pregnant, aged <18 years, discharged “against medical advice,” assigned comfort care on hospitalization, or transferred from another hospital. For patients with multiple hospitalizations, the

first was included. For all analyses, patients who died during hospitalization were excluded. In addition, we excluded patients who were on anticoagulants before admission or were diagnosed with a VTE during hospitalization as there is no equipoise as to whether to anticoagulate those patients on discharge.

On the basis of available data collection resources, some MI-COVID19 hospitals were able to include all patients with COVID-19 who were hospitalized during the study time period. Other hospitals (eg, those with high volumes) used a pseudo-random sampling process to select cases. Pseudo-randomization involved sorting potentially eligible discharges by timestamp of discharge and reviewing patients for inclusion in ascending order on the basis of the minute in which they were discharged and including patients until they reached abstractor capacity.<sup>15</sup>

## Data Collection

Experienced, professional abstractors for other Blue Cross Blue Shield of Michigan collaborative quality initiatives were retrained to collect data on patients with COVID-19 for MI-COVID19.<sup>19</sup> Using standardized data templates and detailed data dictionaries, abstractors collected demographic data, comorbidities, daily anticoagulant use, daily COVID-19 therapy, laboratory data, and stability data (eg, respiratory support).

Patient outcomes, including date outcome occurred, were collected prospectively up to 60 days after hospitalization via medical record review and a postdischarge patient telephone call. To assess patient outcomes, abstractors reviewed the medical record 60 days following discharge to determine whether the patient was deceased. If so, and, if available, cause(s) of death and date of death were abstracted. If no data were available or the patient appeared to be alive 60 days following discharge, the patient was contacted by telephone up to 3 times to obtain additional outcome data, including whether the patient had been diagnosed with a VTE or stroke since hospital discharge. If the telephone respondent noted the patient had died since hospitalization, he/she was asked cause and date of death. To assess VTE events, abstractors reviewed the medical record 60 days following discharge to determine whether there was a confirmed or suspected deep vein thrombosis or pulmonary embolism noted in the medical record and, if so, collect related imaging results and event dates. All data were entered into the MI-COVID19 registry using a structured data collection template. Full definitions of patient outcomes and how they related to MICHELLE trial outcomes are shown in Table S2. As disparities attributable to patient demographics may exist, we report data on sex, race, and ethnicity obtained from the medical record and categorized as noted in Data S1.

## Primary Outcome

Our primary outcome of interest was the proportion of patients hospitalized with COVID-19 (who survived to discharge, were not previously on anticoagulants, and were not diagnosed with VTE during hospitalization) who would be eligible to receive postdischarge VTE prophylaxis with rivaroxaban, according to the MICHELLE trial eligibility/exclusion criteria.

Patients were considered eligible for rivaroxaban if they had an elevated risk for VTE defined using an adaptation of the IMPROVE (International Medical Prevention Registry on Venous Thromboembolism) score, also used in the Medically Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolic Risk trial.<sup>6</sup> Specifically, patients were considered to have an elevated risk for VTE if they had an IMPROVE score  $\geq 4$  or an IMPROVE score of 2 to 3 and a D-dimer  $\geq 1$  time the upper limit of normal (ULN) at that hospital. Because of different D-dimer tests at each hospital, we used  $1 \times \text{ULN}$  as a surrogate for the trial criteria of  $>500 \text{ ng/mL}$ . Other D-dimer thresholds were studied in the sensitivity analyses, described below. Table 1 shows how each element of the IMPROVE score was operationalized in the MI-COVID19 cohort. For patients missing a D-dimer score, D-dimers were imputed (see description below). Because they may have had a contraindication to anticoagulation that we were unable to assess, we excluded patients who received no anticoagulants during hospitalization. Additional MICHELLE trial exclusions and how they were operationalized are shown in Table 2.

**Table 1. IMPROVE Score Definition and Operationalization**

MICHELLE trial IMPROVE score definition	Our definition/operationalization
Previous VTE: 3 points	VTE (DVT/PE) listed as a comorbidity
Known thrombophilia: 2 points	Data unavailable in MI-COVID19
Current lower limb paralysis or paresis: 2 points	Hemiplegia or paraplegia listed as a comorbidity
History of cancer: 2 points	Leukemia, lymphoma, any malignancy without metastasis, or metastatic solid tumor listed as a comorbidity
ICU stay: 1 point	Any day spent in an ICU
Complete immobilization $\geq 1$ d* Trial definition: confined to bed or chair with or without sanitary privileges	All hospitalized patients with COVID-19 Sensitivity analyses: • Defined as ICU patients only • Defined as paralytic use only
Aged $\geq 60$ y: 1 point	Age at admission $>60$ y

DVT indicates deep venous thrombosis; ICU, intensive care unit; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; MICHELLE, Medically Ill Hospitalized Patients for COVID-19 Thrombosis Extended Prophylaxis With Rivaroxaban Therapy; PE, pulmonary embolism; and VTE, venous thromboembolism.

\*Sensitivity analyses occurred with different definitions.

**Table 2. Additional Trial Exclusions and Operationalization**

MICHELLE trial definition/exclusion	Our definition/operationalization
Length of stay <3d	Length of stay <3d
Received standard-dose thromboprophylaxis (LMWH, fondaparinux, or UFH) during hospitalization	Exclude patients who received therapeutic-dose or no anticoagulation at any point during hospitalization
Any prior intracranial hemorrhage or hemorrhagic stroke	Data unavailable in MI-COVID19
Active gastroduodenal ulcer	Peptic ulcer disease listed as comorbidity
Thrombocytopenia (platelet count <75×10 <sup>9</sup> )	Last platelet count during hospitalization <75×10 <sup>9</sup>
Active cancer (excluding skin cancer)	Metastatic solid tumor listed as comorbidity*
Severe renal failure (Cockcroft-Gault CrCl <30)	On dialysis or CrCl <30 based on last creatinine before discharge
Severe liver disease	Moderate or severe liver disease listed as comorbidity
HIV	AIDS or HIV listed as comorbidity
Cardiogenic or septic shock with vasopressor support during initial hospitalization	Required vasopressors at any point during hospitalization*
Drug-drug interactions (with rivaroxaban)	Any documented use of rifampin, clarithromycin, or ritonavir
Significant antiplatelet use (aspirin >162mg/d; clopidogrel, prasugrel, or ticagrelor use)	Excluded patients on clopidogrel or dipyridamole
Bleeding within 3mo before hospitalization; major surgery within 4wk of hospitalization; planned surgery; known coagulopathy or INR >1.5 before discharge; intracranial neoplasm; bilateral amputation; uncontrolled hypertension; IVC filter; tuberculosis; fibrinolysis during hospitalization; daily use of NSAIDs	Data unavailable in MI-COVID19

CrCl indicates creatinine clearance; INR, international normalized ratio; IVC: inferior vena cava; LMWH, low-molecular-weight heparin; MICHELLE: Medically Ill Hospitalized Patients for COVID-19 Thrombosis Extended Prophylaxis With Rivaroxaban Therapy; and UFH, unfractionated heparin.

\*Sensitivity analyses occurred with different definitions.

## Secondary Outcomes

Our secondary outcomes attempted to mirror MICHELLE trial outcomes (Table S2). The main secondary outcome was a composite of symptomatic VTE, pulmonary embolism–related death, nonhemorrhagic stroke, and cardiovascular death at 35 days. Unlike the MICHELLE trial, we did not have 35-day outcome data on symptomatic arterial thromboembolism, myocardial infarction, major adverse limb events, or asymptomatic VTE detected via Doppler venous ultrasound scan or computed tomography angiogram in the MI-COVID19 registry. For the composite clinical outcome, we truncate outcomes at 35 days to be consistent with MICHELLE trial. Secondly, we also report 60-day outcomes. Additional secondary outcomes, consistent with the MICHELLE trial, include the combined outcome of symptomatic VTE and all-cause mortality at 35 days.

## Statistical Analysis

Descriptive statistics were used to characterize the cohort and 35-day outcomes. We also report the percentage of patients who would be eligible for rivaroxaban according to the MICHELLE trial. For patients with an IMPROVE score of 2 to 3 who were missing D-dimer values, we assumed data were missing at random. We used multivariate imputation by fully conditional specification with categorical variables imputed via logistic regression and continuous variables imputed via predictive mean matching. Predictive mean matching uses regression to determine a set of similar patients and then randomly imputes a value from the observed values of those patients.

This method ensures imputed values do not fall outside of the observed distribution. Imputation was based on likely predictors of D-dimer values (ie, age, body mass index, Charlson comorbidity index, platelet value, sex, race, ethnicity, admission from nursing home, previous deep vein thrombosis, heart failure, creatinine clearance, diabetes, cancer, smoking status, highest level of respiratory support, and first level of care on admission). Missing D-dimer data were then imputed through a 10-fold multiple imputation procedure; the mean value from the 10 imputations was then used to classify patients as eligible versus ineligible for rivaroxaban.

## Sensitivity Analysis

We conducted multiple sensitivity analyses using different definitions for each of the MICHELLE trial exclusion criteria. Our primary analysis most closely resembled the MICHELLE trial. We also report what percentage of patients would be eligible for rivaroxaban for the following sensitivity analyses: (1) D-dimer cutoff used for rivaroxaban eligibility in patients with IMPROVE score of 2 to 3 was changed from  $\geq 1 \times \text{ULN}$  to  $\geq 2 \times \text{ULN}$  or  $\geq 4 \times \text{ULN}$ ; (2) complete immobilization  $\geq 1$  day (component of IMPROVE score), defined as all patients with COVID-19 versus just those ever in an intensive care unit versus just those ever on paralytics; and (3) a “most broadly clinically inclusive” group that did not exclude patients with active cancer, those who had shock during hospitalization, or those who received treatment-dose anticoagulation during hospitalization.

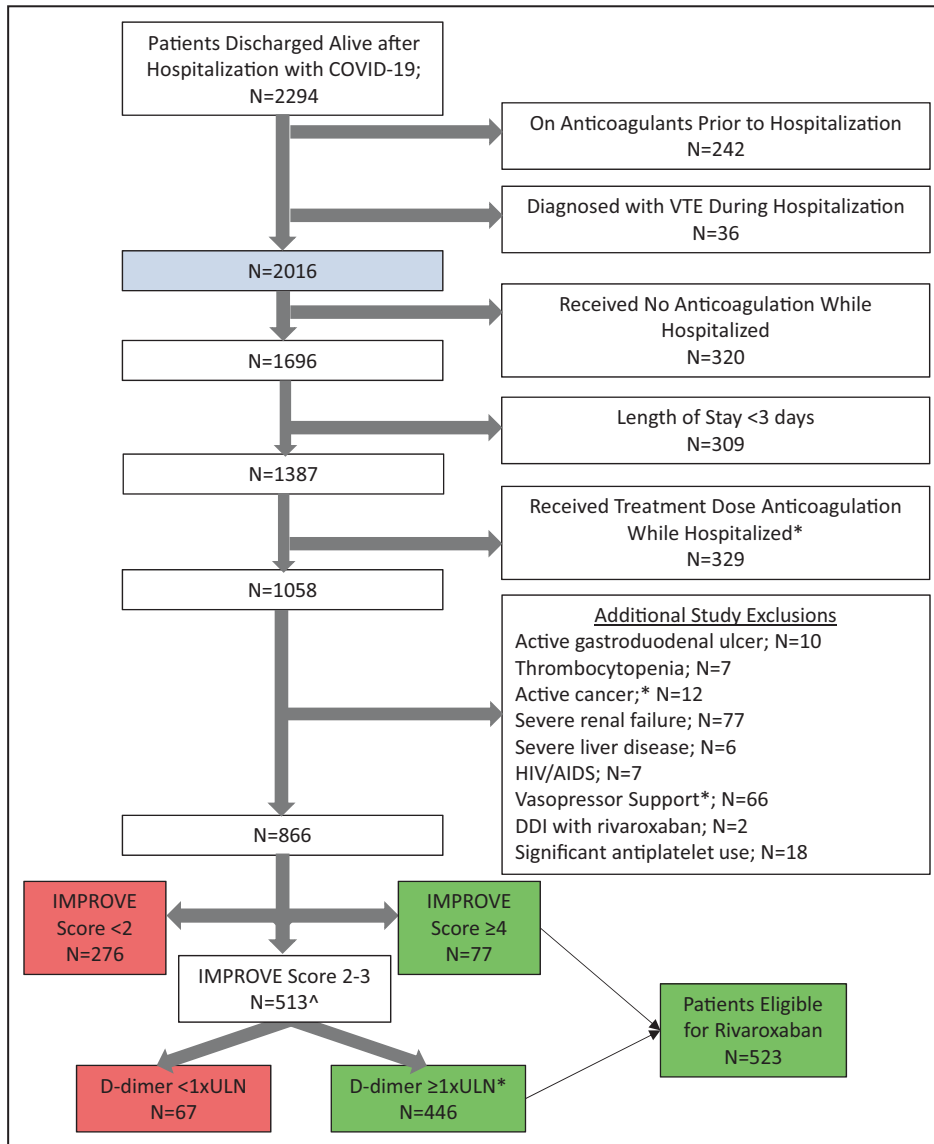
Analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC). We followed Enhancing the Quality and Transparency Of Health Research reporting guidelines (Strengthening the Reporting of Observational Studies in Epidemiology checklist). This study was deemed not regulated by the institutional review board at University of Michigan, and no informed consent was required.

## RESULTS

Between March 7, 2020, and January 23, 2021, a total of 2294 patients in the MI-COVID19 database hospitalized with COVID-19 at 35 hospitals in Michigan

survived until discharge. Of those patients, 242 were on anticoagulants before hospitalization and 36 were diagnosed with a VTE during hospitalization, leaving 2016 patients who could potentially be eligible for new anticoagulant use at discharge.

After exclusions consistent with the MICHELLE trial (Figure 1 provides a detailed flow diagram), 523 patients (25.9% of 2016 patients) were eligible for rivaroxaban. Of the 416 who had discharge anticoagulant data collected, only 13.2% (55/416) were actually prescribed a new anticoagulant at discharge. Compared with patients in the MICHELLE trial, patients potentially eligible for rivaroxaban in MI-COVID19 were older (median age, 69 versus 56–58 years), less likely to have spent time in



**Figure 1. Study inclusion/exclusion diagram.**

\*Sensitivity analyses performed for these exclusions. ^For N=179 patients missing a D-dimer, D-dimer values were calculated using multiple imputation. DDI indicates drug-drug interaction; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; ULN, upper limit of normal; and VTE, venous thromboembolism.

an intensive care unit (30% versus 50%–54%), and had a shorter median length of stay (7 versus 8 days); detailed patient characteristics can be found in Table 3. On sensitivity analyses, the proportion of patients eligible for rivaroxaban at discharge varied from 2.9% to 39.4%, depending on how exclusion and eligibility criteria were operationalized (Figure 2 and Table S3).

Of 523 patients eligible for rivaroxaban per the MICHELLE trial, 4 were missing outcome data. In the remaining 519 patients, the composite 35-day outcome occurred in 1.2% (6/519; Table 4). The secondary outcome of symptomatic VTE plus all cause-mortality at 35 days occurred in 6.2% (32/519). Within 60 days, the composite clinical outcome occurred in 2.9% (15/519) of patients eligible for rivaroxaban, whereas the secondary outcome of symptomatic VTE plus all-cause mortality occurred in 7.9% (41/519). Symptomatic VTE at 60 days occurred in 1.6% (8/519).

## DISCUSSION

In this cohort of >2200 patients hospitalized with COVID-19 in 35 Michigan hospitals, we found 25.9% of patients met the MICHELLE trial's eligibility criteria for receiving posthospital thromboprophylaxis. In our study, 1.2% of patients eligible for posthospital rivaroxaban thromboprophylaxis, per the MICHELLE trial, experienced the composite clinical outcome at 35 days, with 7.9% experiencing symptomatic VTE or all-cause mortality.

When deciding whether to prescribe rivaroxaban thromboprophylaxis at discharge for patients hospitalized with COVID-19, clinicians should consider the MICHELLE trial eligibility criteria, which focused on patients at potentially high risk for VTE after discharge. In our analysis, we found ≈1 in 4 patients discharged with COVID-19 would qualify for rivaroxaban thromboprophylaxis at discharge based on the MICHELLE trial eligibility and exclusion criteria. The largest exclusions were short hospital stays, lack of receipt of prophylactic anticoagulation during hospitalization (much of which may have been inappropriate),<sup>16</sup> and low IMPROVE scores. When broader eligibility/exclusion criteria were used and patients with active cancer, shock, and inpatient use of treatment-dose anticoagulation were considered eligible, up to 39.4% of patients would be eligible for rivaroxaban. Thus, the MICHELLE trial results may apply to many patients hospitalized with COVID-19. That only 13.2% of patients eligible per MICHELLE trial criteria received prophylactic anticoagulation implies an opportunity for improvement. Given the many exclusions in the MICHELLE trial meant to reduce unnecessary bleeding risk, clinicians must thoughtfully estimate and weight both thrombotic and bleeding risk in the posthospital period when

**Table 3. Characteristics of Patients Eligible for Rivaroxaban at Discharge per MICHELLE Trial Criteria**

Characteristic	Eligible for rivaroxaban N = 523
Demographics	
Age, y; median (IQR)	68.6 (62.0–77.8)
Aged ≥75 y, n (%)	163 (31.2)
Women, n (%)	260 (49.7)
Men, n (%)	263 (50.3)
Race, n (%)	
Black	197 (37.7)
White	273 (52.2)
Asian	11 (2.1)
Other**	14 (2.7)
Unknown	28 (5.4)
Ethnicity, n (%)	
Non-Hispanic	457 (87.4)
Hispanic	34 (6.5)
Unknown	32 (6.1)
IMPROVE score, n (%)	
2–3	446 (85.3)
≥4	77 (14.7)
Comorbidities, n (%)	
Body mass index, mean (SD), kg/m <sup>2</sup>	30.8 (7.7)
Skilled nursing facility before hospitalization	57 (10.9)
Aspirin use before hospitalization	35 (6.7)
History of VTE*	16/501 (3.2)
Charlson comorbidity score, median (IQR)	1 (0–3)
Peripheral vascular disorders <sup>†</sup>	29 (5.5)
Cerebrovascular disease	50 (9.6)
Cardiovascular disease	106 (20.3)
Congestive heart failure/cardiomyopathy	58 (11.1)
History of myocardial infarction	18 (3.4)
Creatinine clearance, ml/min 30–≤50 <sup>‡</sup>	61/521 (11.7)
Creatinine clearance ≥50 <sup>‡</sup>	448/521 (86.0)
Hypertension	340 (65.0)
Diabetes	184 (35.2)
Cancer <sup>§</sup>	65 (12.4)
Smoking history	
Never	305 (58.3)
Prior	164 (31.4)
Current/active	21 (4.0)
Unknown	33 (6.3)
Severity of illness, n (%)	
Length of hospital stay, d; median (IQR)	7 (4–10)
Length of hospital stay, d; mean (SD)	7.9 (4.9)
Received care in an ICU	155 (29.6)
Highest level of respiratory support	
No supplemental oxygen	107 (20.5)

(Continued)

**Table 3. Continued**

Characteristic	Eligible for rivaroxaban N = 523
Low-flow oxygen	313 (59.8)
Heated high-flow nasal cannula	67 (12.8)
Noninvasive mechanical ventilation	12 (2.3)
Mechanical ventilation	24 (4.6)
Required new dialysis	2 (0.4)
COVID-19–related treatments during hospitalization, n (%)	
Hydroxychloroquine	218 (41.7)
Hydroxychloroquine and azithromycin	154 (29.4)
Remdesivir	77 (14.7)
Interleukin-6 receptor inhibitor	12 (2.3)
Corticosteroids	248 (47.4)
Most abnormal admission laboratory findings (in first 2 d of hospitalization)	
D-dimer, $\times$ ULN, median (IQR) <sup>†</sup>	1.90 (1.28–3.27)
No D-dimer obtained in first 2 d	252 (48.2)
D-dimer above $>1\times$ ULN, n (%)	252/271 (93.0)
D-dimer above $>2\times$ ULN, n (%)	129/271 (47.6)
D-dimer above $>4\times$ ULN, n (%)	50/271 (18.5)
Ferritin, median (IQR), ng/mL	533 (222–1039)
CRP, median (IQR), mg/dL	12.2 (6.0–22.7)
Creatinine, median (IQR), mg/dL <sup>‡</sup>	1.07 (0.83–1.42)
Lowest platelet count, median (IQR), 1000/ $\mu$ L	187 (150–249)
Most abnormal laboratory findings (entire hospitalization)	
D-dimer, median (IQR), $\times$ ULN <sup>†,§</sup>	2.36 (1.53–4.20)
Ferritin, median (IQR), ng/mL	658 (293–1283)
CRP, median (IQR), mg/dL	15.8 (7.5–34.2)
D-dimer above $>1\times$ ULN, n (%) <sup>†</sup>	518 (99.0)
D-dimer above $>2\times$ ULN, n (%) <sup>†</sup>	347 (66.3)
D-dimer above $>4\times$ ULN, n (%) <sup>†</sup>	140 (26.8)
Prophylactic anticoagulant given during hospitalization <sup>¶</sup>	
Enoxaparin (Lovenox) 30–40 mg/d	341 (65.2)
Enoxaparin (Lovenox) 30–40 mg BID	101 (19.3)
Fondaparinux (Arixtra) 2.5 mg/d	5 (1.0)
Heparin $\leq 15000$ daily units	165 (31.5)
Heparin $>15000$ daily units	2 (0.4)
Apixaban (with prophylactic intent)	5/484 (1.0)
Intravenous heparin (with prophylactic intent)	4/484 (0.8)
New anticoagulant prescribed at discharge, n (%)	55/416 (13.2)
Apixaban (Eliquis)	19/416 (4.6)
Dabigatran (Pradaxa)	0/416 (0)
Edoxaban (Savaysa)	0/416 (0)
Enoxaparin (Lovenox)	13/416 (3.1)
Rivaroxaban (Xarelto)	3/416 (0.7)

(Continued)

**Table 3. Continued**

Characteristic	Eligible for rivaroxaban N = 523
Warfarin (Coumadin)	0/416 (0)

Data are given as number (percentage) or number/total (percentage), unless otherwise indicated. BID indicates twice daily; CRP, C-reactive protein; ICU, intensive care unit; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; IQR, interquartile range; MICHELLE, Medically Ill Hospitalized Patients for COVID-19 Thrombosis Extended Prophylaxis With Rivaroxaban Therapy; ULN, upper limit of normal; and VTE, venous thromboembolism.

<sup>†</sup>Data missing for all patients with data collection before May 3, 2020.

<sup>‡</sup>Peripheral vascular disorders include amputations from peripheral vascular disease, any arterial occlusive disease, or history of a vascular surgery related to peripheral vascular disease.

<sup>§</sup>Excludes 2 patients on dialysis.

<sup>¶</sup>Cancer includes any nonskin solid or hematologic malignancy with or without metastasis.

<sup>††</sup>D-dimer is reported in terms of number of times the ULN provided by the laboratory at each hospital. Given variation in reporting, values were capped at 10 times ULN.

<sup>†††</sup>Includes imputed values.

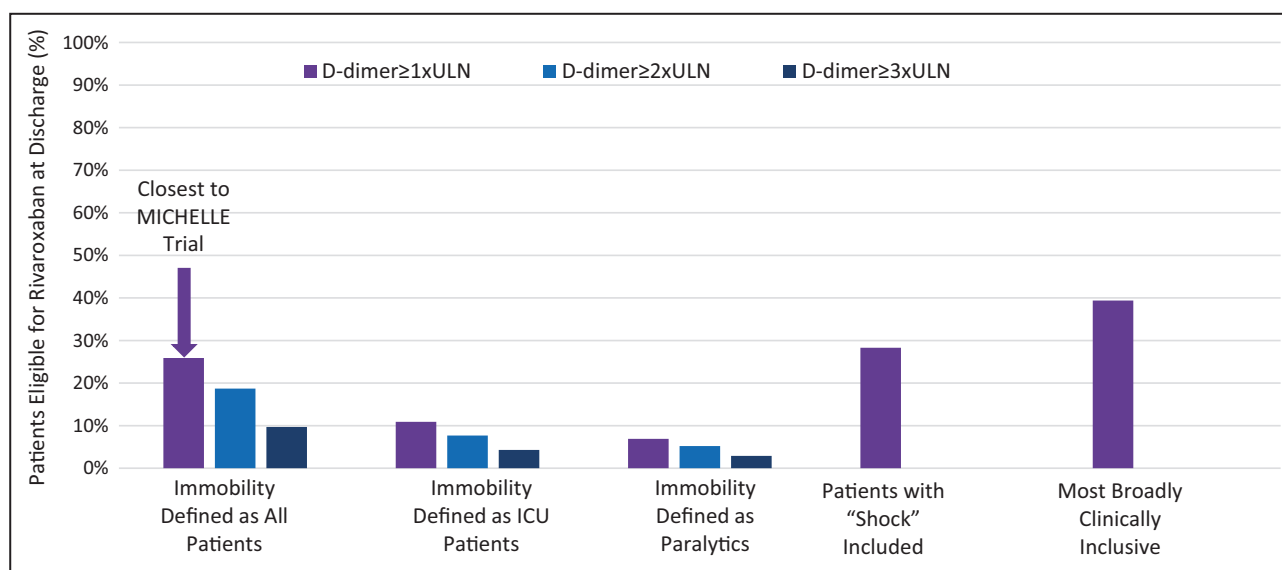
<sup>††††</sup>Patients could receive multiple prophylactic anticoagulants during hospitalization. Numbers may add up to  $>100\%$ .

<sup>†††††</sup>Patient demographic information indicates the patient's race is a race other than Black, White, or Asian.

determining if rivaroxaban thromboprophylaxis is appropriate for an individual patient.

In regards to clinical event rates, we found our composite clinical outcomes to be numerically lower than those found in the MICHELLE trial control groups, yet similar to meta-analytic estimates among patients with COVID-19 and seminal observational studies before COVID-19.<sup>11,20</sup> Notably, we did not routinely perform diagnostic imaging on patients who were asymptomatic and therefore did not collect data on asymptomatic VTE, a large driver of high event numbers for the MICHELLE trial. The fact that we found only 3 additional VTEs (0.6%) at 60 (versus 35) days suggests that asymptomatic VTEs detected at routine screening may not progress to symptomatic VTE in the posthospitalized medically ill population. Notably, we found that the MICHELLE trial's main secondary outcome of symptomatic VTE and all-cause mortality appeared similar in our cohort to that seen in the trial's control group and higher than what was seen in the MICHELLE trial's rivaroxaban group. Ongoing trials (eg, Accelerating COVID-19 Therapeutic Interventions and Vaccine-4c and Helping Alleviate the Longer-Term Consequences of COVID-19) are underway to better understand the potential benefits of postdischarge VTE prophylaxis of apixaban in patients hospitalized with COVID-19. Future work should seek to evaluate the cost-effectiveness and number needed to treat with postdischarge rivaroxaban to improve outcomes in hospitalized patients with COVID-19.

Our study should be considered in the context of limitations. First, we did not collect all the outcomes collected in the MICHELLE trial, and the primary purpose



**Figure 2. Patients with COVID-19 eligible for rivaroxaban at discharge across sensitivity analyses (N=2016 patients).**

The percentage of patients discharged alive from a COVID-19 hospitalization (who were not on anticoagulants before hospitalization or developed a venous thromboembolism during hospitalization) who would be eligible for rivaroxaban at discharge is shown. Each bar represents a different sensitivity analysis. The bar marked with an arrow most closely resembles the Medically Ill Hospitalized Patients for COVID-19 Thrombosis Extended Prophylaxis With Rivaroxaban Therapy (MICHELLE) trial. The colors reflect the D-dimer cutoff for eligibility for rivaroxaban at discharge for patients with an IMPROVE (International Medical Prevention Registry on Venous Thromboembolism) score of 2 to 3. The most broadly inclusive category does NOT exclude shock, active malignancy, or patients who received therapeutic anticoagulation during hospitalization (which are exclusions for the MICHELLE trial). ICU indicates intensive care unit; and ULN, upper limit of normal.

of MI-COVID19 was not to obtain outcome data. In addition, some outcomes included patient-reported outcomes, which requires patients for ascertainment and may affect the validity and reliability of outcomes. For

these reasons, outcome ascertainment was limited. Most MICHELLE trial outcomes were rare, with the exception of asymptomatic VTE, which is not routinely assessed in clinical practice. Similarly, our eligibility and

**Table 4. Outcomes: Primary Inclusion Group**

Outcomes at 35 d	MICHELLE trial: rivaroxaban (N=159)	MICHELLE trial: control (N=159)	MI-COVID19 database: patients eligible for rivaroxaban (N=519)*
Symptomatic VTE	0.63 (1)	3.14 (5)	1.0 (5/519)
Symptomatic DVT	0	1.89 (3)	0 (0/519)
Symptomatic PE	0.63 (1)	1.26 (2)	1.0 (5/519)
Fatal PE	0	1.89 (3)	0 (0/519)
Nonhemorrhagic stroke	0	0	0 (0/519)
Cardiovascular death	0	0.63 (1)	0.2 (1/519)
Any of the above (main secondary outcome)	0.63 (1)	5.66 (9)	1.2 (6/519)
Symptomatic arterial thromboembolism	0	0.63 (1)	Not collected
Myocardial infarction	0	0	Not collected
Major adverse limb events	0	0	Not collected
Asymptomatic VTE detected at DVT scan	1.89 (3)	0.63 (1)	Not collected
Asymptomatic VTE detected at CT angiography	0.63 (1)	2.52 (4)	Not collected
Any of the above (MICHELLE trial primary outcome)	3.14 (5)	9.43 (15)	1.2 (6/519)
Symptomatic VTE+all-cause mortality (MICHELLE trial main secondary outcome)	2.52 (4)	5.66 (9)	6.2 (32/519)
All-cause mortality	1.89 (3)	2.5 (4)	5.2 (27/519)

Data are given as percentage (number) or percentage (number/total). CT indicates computed tomography; DVT, deep vein thrombosis; MICHELLE, Medically Ill Hospitalized Patients for COVID-19 Thrombosis Extended Prophylaxis With Rivaroxaban Therapy; PE, pulmonary embolism; and VTE, venous thromboembolism.

\*Four patients missing outcome data were excluded.



exclusion definitions were not identical to those used in the MICHELLE trial, and our methods for operationalizing definitions (eg, ascertaining IMPROVE scores) could skew our reporting of patients eligible for rivaroxaban. Third, our study represents 2020 care in the state of Michigan, much of it during hospital surge/crisis times. This likely skews our mortality data higher than it would be in 2021 (or beyond) when more COVID-19 therapeutics were available. It also represents a population of patients who were infected with the original COVID-19 virus, not the highly infectious Delta variant that was predominant in the United States in 2021. Finally, our study is retrospective and limited by the usual restrictions created by relying on medical record documentation and physician- and patient-reported outcome capture. Study strengths include the collection of data on a diverse, real-life study population, the ability to evaluate eligibility criteria across a host of sensitivity analyses, and a large study population. All of our outcomes include patient-reported data, and we collected outcomes through 60 days, allowing us to be more confident in our analyses.

In conclusion, we found that, by MICHELLE trial criteria,  $\approx 1$  in 4 patients hospitalized with COVID-19 would be eligible for rivaroxaban at discharge. That number likely varies based on how eligibility and exclusion criteria are operationalized. Regardless, with only 13% of patients actually receiving postdischarge prophylaxis, there is a potential opportunity for improvement in care.

## ARTICLE INFORMATION

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### Supplemental Material

Data S1  
Tables S1–S3

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## **SUPPLEMENTAL MATERIAL**

**Data S1.**

**Michigan Hospital Medicine Safety (HMS) Collaborative  
Definition of Sex, Race, and Ethnicity**

**Sex**

Instructions: Review the medical record to determine the gender (or sex) of the patient. This is a required field and the form cannot be submitted without an entry in this field. Select one of the following:

- *“Male”* if the patient is categorized as a man in the medical record.
- *“Female”* if the patient is categorized as a woman in the medical record.
- *“Unknown”* if unknown.

**Ethnicity**

Instructions: Review the medical record to determine the patient’s ethnicity. Select one of the following:

- *“Hispanic or Latino”* if patient demographic information indicates patient is of Hispanic descent. The US Census Bureau states that *“People who identify their origin as Spanish, Hispanic, or Latino may be of any race.”*
- *“Non-Hispanic or Latino”* if patient demographic information indicates patient is not of Hispanic descent.
- *“Unknown”* if ethnicity is not reported in the medical record.

**Race**

Instructions: Review the medical record to determine the patient’s race. Select one of the following:

- *“American Indian or Alaskan Native”* if patient demographic information indicates patient is Native American, American Indian, or Alaska Native.
- *“Arab and Chaldean Ancestries”* if the patient demographic information indicate patient is of Arab or Chaldean Ancestries.
- *“Asian”* if patient demographic information indicates Asian.
- *“Black or African American”* if patient demographic information indicates patient is black or African American.
- *“Native Hawaiian or Pacific Islander”* if patient demographic information indicates patient is Native Hawaiian or Pacific Islander.
- *“White or Caucasian”* if patient demographic information indicates patient is white or Caucasian.
- *“Other”* if patient demographic information indicates the patient is a race other than what is listed above.
- *“Unknown”* if patient’s race is not indicated in the medical record.

**Table S1.** Characteristics of Participating MiCOVID Hospitals vs. HMS Hospitals that Did Not Participate

Variable	MiCOVID 19 Hospitals (n=35)	2020 HMS Hospitals that did not Participate in MiCOVID19 (n=10)	P-value
Academic hospital, N (%) <sup>*</sup>	30 (85.7%)	9 (90.0%)	0.99
Number of hospitalists, median (IQR) <sup>†</sup>	20 (11-37.5)	20.5 (6-53)	0.99
Profit Type, N(%) <sup>‡</sup>			
Non-profit	29 (82.9%)	8 (80.0%)	0.04
For profit	6 (17.1%)	0 (0)	
Governmental	0 (0%)	2 (20.0%)	
Bed Size, N(%) <sup>§</sup>			
Median (IQR)	317 (191-443)	342.5 (96-422)	0.72

Hospitals that participated in MiCOVID19 are compared to hospitals that were participating in HMS in 2020 but did not participate in MiCOVID19. P-values were calculated from chi-squared or t-tests, as appropriate, with P<0.05 considered significant. Abbreviations: IQR, inter-quartile range; HMS, Michigan Hospital Medicine Safety Consortium

<sup>\*</sup> Academic hospital status from the American Medical Association's FREIDA Institution Directory

<sup>†</sup> Data are self-reported from the November 2020 hospital survey. 3 MiCOVID19 hospitals did not provide data.

<sup>‡</sup> Profit status obtained from data.medicare.gov.

<sup>§</sup> Hospital bed size was obtained from the 2015 Michigan Certificate of Need Annual Survey

**Table S2.** Trial Definitions and Operationalization

<b>Trial Definition</b>	<b>Our definition/operationalization</b>
Symptomatic VTE	Medical record reviewed by trained abstractors. Answer yes to any of the following questions: “Was the patient diagnosed with a confirmed or suspected DVT during the 60 days following the hospital encounter?” “Was the patient diagnosed with a confirmed or suspected PE during the 60 days following the hospital encounter?” Data truncated at 35 days post-discharge.
Fatal PE	Medical record reviewed by trained abstractors. Answer yes to the question “Is the patient deceased within the 60 days post discharge?” AND answer “VTE (include DVT or PE)” to the question “Were any of the following listed as the cause of death?” Data truncated at 35 days post-discharge.
VTE detected at DVU scan or CT angiography	Data unavailable in MI-COVID19
Symptomatic arterial thromboembolism	Data unavailable in MI-COVID19
Myocardial infarction	Data unavailable in MI-COVID19
Non-hemorrhagic stroke	Medical record reviewed by trained abstractors. Answer yes to the question, “Was the patient diagnosed with a stroke/CVA in the 60 days following the hospital encounter?). Exclude patients with an answer of “hemorrhagic” to the question “Select the type of stroke/CVA.” Data truncated at 35 days post-discharge.
Major adverse limb events	Data unavailable in MI-COVID19
Cardiovascular death	Medical record reviewed by trained abstractors. Answer yes to the question “Is the patient deceased within the 60 days post discharge?” AND answer “presumed cardiac arrhythmia,” “heart failure,” “myocardial infarction,” or “stroke” to the question “Were any of the following listed as the cause of death?” Data truncated at 35 days post-discharge.
Composite of Above (primary outcome)	Composite of Above (primary outcome) Data truncated at 35 days post-discharge.
35-day all-cause mortality	Medical record reviewed by trained abstractors. Answer yes to the question “Is the patient deceased within the 60 days post discharge?” Data truncated at 35 days post-discharge.

Abbreviations: VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; DVU, diagnostic vascular ultrasound; CT, computed tomography; CVA, cerebrovascular accident.

**Table S3.** Number of Patients Eligible for Rivaroxaban at Discharge across Sensitivity Analyses, N=2,016 patient

	Immobility Defined as All Patients with COVID-19			Immobility Defined as ICU			Immobility Defined as Paralytics			Shock Included	Most Broadly Clinically Inclusive	
	D-dimer $\geq 1xULN^*$	D-dimer $\geq 2xULN$	D-dimer $\geq 4xULN$	D-dimer $\geq 1xULN$	D-dimer $\geq 2xULN$	D-dimer $\geq 4xULN$	D-dimer $\geq 1xULN$	D-dimer $\geq 2xULN$	D-dimer $\geq 4xULN$			
<b>MICHELLE Trial Exclusions</b>												
Active Cancer Included <sup>†</sup>												X
Patients who Received Treatment-Dose Anticoagulation During Hospitalization Included												X
Shock Included										X		X
<b>D-dimer Cutoff Used for Patients with IMPROVE Score of 2-3<sup>‡</sup></b>												
$\geq 1xULN$	X			X			X			X		X
$\geq 2xULN$		X			X			X				
$\geq 4xULN$			X			X			X			
<b>Definition of Immobility Used for IMPROVE Score</b>												
All patients	X	X	X							X		X
ICU patients				X	X	X						
On paralytics							X	X	X			
Eligible for rivaroxaban at Discharge	523	376	196	220	156	86	139	105	59	570		794
Percent Eligible of COVID-19 Discharges Not Already on Anticoagulants <sup>§</sup>	25.9%	18.7%	9.7%	10.9%	7.7%	4.3%	6.9%	5.2%	2.9%	28.3%		39.4%

\* Primary analysis. Most closely reflects patient population from MICHELLE trial

<sup>†</sup> Operationalized as patients with metastatic cancer listed as a comorbid condition. Patients with any of the following listed as comorbid conditions were included in all analyses: leukemia, lymphoma, any malignancy without metastasis.

<sup>‡</sup> For N=179 patients missing a D-dimer, D-dimer values were calculated using multiple imputation.

<sup>§</sup> Includes all hospitalized patients that survived to hospital discharge and were not on anticoagulation prior to hospitalization or developed a VTE requiring anticoagulation during hospitalization.

Abbreviations: ICU, intensive care unit; ULN, upper limit of normal