Table 6a. Anticoagulant Therapy: Selected Clinical Trial Data

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The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for anticoagulant therapy. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
ATTACC/ACTIV-4a/REMAP-CAP: Multiplatform, Open-Label RCT of Therapeutic Anticoagulation in Noncritically Ill, Hospitalized Patients With COVID-19 in 9 Countries[1]		

Key Inclusion Criterion
• Hospitalized with laboratory-confirmed SARS-CoV-2 infection without need for HFNC oxygen, NIV, MV, vasopressors, or inotropes
Key Exclusion Criteria
• Hospital discharge expected in ≤72 hours
• Need for therapeutic anticoagulation or dual antiplatelet therapy
• High bleeding risk
Interventions
• Therapeutic UFH or LMWH for 14 days or until hospital discharge, whichever came first (n = 1,190)
• SOC, which included prophylactic UFH or LMWH (n = 1,054)
Primary Endpoint
• Organ support-free days by Day 21, as measured by an OS
Key Secondary Endpoints
• Survival until hospital discharge
• Hospital LOS
• Thrombosis or major bleeding events
	Participant Characteristics
	• Median age 59 years; 59% men; median BMI 30
	• 52% with HTN; 30% with DM; 11% with CVD
	• 66% required low-flow oxygen.
	• D-dimer level:
	  • 48.4% <2 times ULN
	  • 28.4% ≥2 times ULN
	  • 23.1% unknown
	• 62% on corticosteroids; 36% on RDV
	Primary Outcomes
	• Therapeutic anticoagulation was superior to SOC for organ support-free days (aOR 1.27; 95% CrI, 1.03–1.58; 99% posterior probability).
	• 4% absolute difference in survival until hospital discharge without organ support that favored therapeutic arm (95% CrI, 0.5–7.2)
	• Outcome was consistent across D-dimer stratum.
	Secondary Outcomes
	• Survival until hospital discharge: 92% in both arms
	• No difference between arms in hospital LOS (aOR 1.03; 95% CrI, 0.94–1.13)
	• Thrombosis: 1% in therapeutic arm vs. 2% in SOC arm
	• Major bleeding events: 2% in therapeutic arm vs. 1% in SOC arm
		Key Limitations
		• Open-label study
		• Dose for anticoagulation varied in SOC arm (27% received intermediate dose of thromboprophylaxis).
		• Inclusion criteria for hospital LOS and ICU-level care differed across trials.
		• Trial only enrolled 17% of screened patients.
		Interpretation
		• Therapeutic heparin increased the number of organ support-free days and decreased the number of patients requiring organ support.
		• Therapeutic heparin did not significantly affect hospital LOS or the number of major thrombosis events or deaths.
		• Major bleeds occurred 1% more frequently in the therapeutic arm than in the SOC arm.

Methods	Results	Limitations and Interpretation
RAPID: Open-Label RCT of Therapeutic Heparin in Moderately Ill, Hospitalized Patients With COVID-19 in 6 Countries[2]		

Key Inclusion Criteria
• Hospitalized with COVID-19 and D-dimer level ≥2 times ULN or any elevated D-dimer level and SpO_2 ≤93% on room air
• Hospitalized <5 days
Key Exclusion Criteria
• Need for therapeutic anticoagulation
• Receiving dual antiplatelet therapy
• High bleeding risk
Interventions
• Therapeutic UFH or LMWH for 28 days or until hospital discharge or death (n = 228)
• Prophylactic UFH or LMWH for 28 days or until hospital discharge or death (n = 237)
Primary Endpoint
• Composite of ICU admission, NIV or MV, or death at 28 days
Key Secondary Endpoints
• All-cause death at 28 days
• Mean number of organ support-free days
• VTE
• Major bleeding events
• Mean number of hospital-free days alive
	Participant Characteristics
	• Median age 60 years; 57% men; mean BMI 30
	• 48% with HTN; 34% with DM; 7% with CVD
	• 91% with hypoxia; 6% received HFNC oxygen.
	• D-dimer level:
	  • 49% <2 times ULN
	  • 51% ≥2 times ULN
	• 69% on corticosteroids
	Primary Outcome
	• Composite of ICU admission, NIV or MV, or death at 28 days: 16% in therapeutic arm vs. 22% in prophylactic arm (OR 0.69; 95% CI, 0.43–1.10)
	Secondary Outcomes
	• All-cause death at 28 days: 2% in therapeutic arm vs. 8% in prophylactic arm (OR 0.22; 95% CI, 0.07–0.65)
	• Mean number of organ support-free days: 26 in therapeutic arm vs. 24 in prophylactic arm (OR 1.41; 95% CI, 0.9–2.21)
	• No difference between arms for VTE (1% in therapeutic arm vs. 3% in prophylactic arm) or major bleeding events (1% in therapeutic arm vs. 2% in prophylactic arm)
	• Mean number of hospital-free days alive: 20 in therapeutic arm vs. 18 in prophylactic arm (OR 1.09; 95% CI, 0.79–1.50)
		Key Limitations
		• Open-label study
		• Trial only enrolled 12% of screened patients.
		Interpretation
		• Compared to prophylactic heparin, therapeutic heparin reduced mortality (a secondary endpoint) but had no effect on the primary composite endpoint of ICU admission, the need for NIV or MV, or death up to 28 days.
		• There were no differences between the arms in the percentages of patients who experienced VTE or major bleeding events.

Methods	Results	Limitations and Interpretation
HEP-COVID: Open-Label RCT of Therapeutic Heparin in High-Risk, Hospitalized Patients With COVID-19 in the United States[3]		

Key Inclusion Criteria
• Hospitalized with COVID-19 and required supplemental oxygen
• D-dimer level >4 times ULN or sepsis-induced coagulopathy score of ≥4
• Hospitalized <72 hours
Key Exclusion Criteria
• Need for therapeutic anticoagulation
• Receiving dual antiplatelet therapy
• High bleeding risk
• CrCl <15 mL/min
Interventions
• Therapeutic LMWH until hospital discharge or primary endpoint met (n = 129)
• Usual care of prophylactic or intermediate-dose LMWH until hospital discharge or primary endpoint met (n = 124)
Primary Endpoint
• Composite of VTE, ATE, or death from any cause within 32 days of randomization
Key Safety Endpoint
• Major bleeding events within 32 days
	Participant Characteristics
	• Median age 67 years; 54% men; mean BMI 30
	• 60% with HTN; 37% with DM; 75% with CVD
	• 64% received oxygen via nasal cannula; 15% received HFNC oxygen or NIV; 5% received MV.
	• 80% on corticosteroids
	Primary Outcomes
	• Composite of VTE, ATE, or death within 32 days: 29% in therapeutic arm vs. 42% in usual care arm (relative risk 0.68; 95% CI, 0.49–0.96)
	  • Thrombotic events: 11% in therapeutic arm vs. 29% in usual care arm (relative risk 0.37; 95% CI, 0.21–0.66)
	  • Death: 19% in therapeutic arm vs. 25% in usual care arm (relative risk 0.78; 95% CI, 0.49–1.23)
	• Non-ICU stratum composite of VTE, ATE, or death within 32 days: 17% in therapeutic arm vs. 36% in usual care arm (relative risk 0.46; 95% CI, 0.27–0.81)
	Safety Outcomes
	• Major bleeding events within 32 days: 5% in therapeutic arm vs. 2% in usual care arm (relative risk 2.88; 95% CI, 0.59–14.02)
	  • Non-ICU stratum major bleeding events within 32 days: 2% in both arms
		Key Limitations
		• Open-label study
		• Trial only enrolled 2% of screened patients.
		Interpretation
		• Compared to usual care, therapeutic LMWH reduced the incidence of VTE, ATE, and death.
		• Among patients who were not in the ICU, therapeutic LMWH significantly reduced the percentage of patients who experienced thrombotic events and did not increase the percentage of patients who experienced major bleeding events.

Methods	Results	Limitations and Interpretation
ACTION: Open-Label RCT of Therapeutic Rivaroxaban in Hospitalized Patients With COVID-19 in Brazil[4]		

Key Inclusion Criteria
• Hospitalized with COVID-19 and elevated D-dimer level
• Symptoms for ≤14 days
Key Exclusion Criteria
• Need for therapeutic anticoagulation
• CrCl <30 mL/min
• Receiving P2Y12 inhibitor therapy or aspirin >100 mg
• High bleeding risk
Interventions
• Therapeutic anticoagulation for 30 days: rivaroxaban 15 mg or 20 mg once daily; if clinically unstable, enoxaparin 1 mg/kg twice daily or UFH (n = 311)
• Usual care prophylactic anticoagulation with enoxaparin or UFH during hospitalization (n = 304)
Primary Endpoint
• Hierarchical composite of time to death, hospital duration, or oxygen use duration by Day 30
Key Secondary Endpoints
• Thrombosis, with and without all-cause death
• Death by Day 30
• Bleeding events
	Participant Characteristics
	• Median age 57 years; 60% men; mean BMI 30
	• 49% with HTN; 24% with DM; 5% with CAD
	• Critically ill: 7% in therapeutic arm vs. 5% in usual care arm
	• 75% required oxygen: 60% received low-flow oxygen; 8% received HFNC oxygen; 1% received NIV; 6% received MV.
	• 83% on corticosteroids
	Primary Outcome
	• No difference between arms in the composite of time to death, hospital duration, or oxygen use duration by Day 30 (win ratio 0.86; 95% CI, 0.59–1.22)
	Secondary Outcomes
	• No difference between therapeutic and usual care arms in:
	  • Thrombosis: 7% vs. 10%
	  • Death by Day 30: 11% vs. 8%
	• Any bleeding events: 12% in therapeutic arm vs. 3% in usual care arm
	• Major bleeding events: 3% in therapeutic arm vs. 1% in usual care arm
	• Clinically relevant, nonmajor bleeding events: 5% in therapeutic arm vs. 1% in usual care arm
		Key Limitations
		• Open-label study
		• Trial only enrolled 18% of screened patients.
		• Therapeutic rivaroxaban was administered for a longer duration than prophylactic anticoagulation (30 days vs. a mean duration of 8 days).
		Interpretation
		• When compared with usual care, therapeutic rivaroxaban did not reduce mortality, hospital duration, oxygen use duration, or the percentage of patients who experienced thrombosis.
		• Patients who received therapeutic rivaroxaban had more clinically relevant, nonmajor bleeding events than those who received usual care.
		• The longer duration of therapy in the therapeutic arm may have influenced the difference in bleeding events.

Methods	Results	Limitations and Interpretation
FREEDOM: RCT of Anticoagulation Strategies in Noncritically Ill Patients Who Were Hospitalized With COVID-19 in 10 Countries[5]		
Key Inclusion Criterion • Hospitalized with symptomatic COVID-19 for <48 hours **Key Exclusion Criteria** • Need for therapeutic anticoagulation • CrCl <30 mL/min • Receiving P2Y12 inhibitor therapy or aspirin >100 mg per day • Anticipated hospitalization for <72 hours **Interventions** • Therapeutic apixaban 5 mg twice daily (n = 1,121) • Therapeutic enoxaparin 1 mg/kg twice daily (n = 1,136) • Usual care prophylactic enoxaparin (n = 1,141) **Primary Endpoint** • 30-day composite of all-cause mortality, need for ICU-level care, systemic thromboembolism, or ischemic stroke. Endpoint assessed for the combined therapeutic arms vs. the prophylactic arm. **Key Secondary Endpoints** • 30-day all-cause mortality • BARC type 3 or 5 bleeding events	**Participant Characteristics** • Median age 52 years; 59% men; mean BMI 26 • 32% with HTN; 19% with DM • 22% on corticosteroids; 10% on RDV **Primary Outcome** • 30-day composite outcome: 11.3% in combined therapeutic arms vs. 13.2% in prophylactic arm (HR 0.85; 95% CI, 0.69–1.04; $P = 0.11$) • Primary endpoint was not statistically significant when therapeutic enoxaparin or apixaban were compared to prophylactic enoxaparin. **Secondary Outcomes** • 30-day all-cause mortality: 4.9% in therapeutic enoxaparin arm vs. 7.0% in prophylactic enoxaparin arm (HR 0.69; 95% CI, 0.49–0.99) • 30-day all-cause mortality: 5.0% in therapeutic apixaban arm vs. 7.0% in prophylactic enoxaparin arm (HR 0.7; 95% CI, 0.49–0.99) • BARC type 3 or 5 bleeding events: 0.4% in combined therapeutic arms vs. 0.1% in prophylactic arm (IRR 3.96; 95% CI, 0.50–31.27)	**Key Limitations** • Open-label study • Trial was terminated early due to slow recruitment (3,452 of 3,600 planned patients recruited). • Minimal treatment with RDV or DEX as SOC for COVID-19 **Interpretation** • When compared with prophylactic enoxaparin, therapeutic apixaban and therapeutic enoxaparin did not reduce 30-day mortality, the need for ICU-level care, or the occurrence of thromboembolism or ischemic stroke. • Fewer patients died in the therapeutic enoxaparin and therapeutic apixaban arms than in the prophylactic enoxaparin arm. • There were no statistically significant differences between the arms in the percentages of patients who experienced severe bleeding events.

Methods	Results	Limitations and Interpretation
COVID-PACT: Open-Label RCT of Full-Dose Versus Prophylactic-Dose Anticoagulation in Adults With COVID-19 Who Were Receiving Intensive Care Unit-Level Care in the United States[6]		
Key Inclusion Criteria • Aged ≥18 years • Acute SARS-CoV-2 infection • Required ICU-level care for ≤96 hours prior to randomization **Key Exclusion Criteria** • Ongoing or planned use of full-dose anticoagulation or dual antiplatelet therapy • High bleeding risk • History of HIT • Ischemic stroke within 2 weeks **Interventions** • Full-dose anticoagulation until Day 28 or hospital discharge, whichever came first (n = 197) • Prophylactic anticoagulation (n = 193) • Eligible patients were also randomized 1:1 to receive clopidogrel or no antiplatelet therapy (n = 292) **Primary Endpoint** • Composite of VTE or ATE events by hospital discharge or Day 28. Events included death due to VTE or ATE, PE, clinically evident DVT, MI, ischemic stroke, systemic embolic event or acute limb ischemia, and clinically silent DVT. **Key Secondary Endpoint** • Individual outcomes listed above, with the exception of clinically silent DVT **Key Safety Endpoints** • Fatal or life-threatening bleeding events • Moderate or severe bleeding events	**Participant Characteristics** • Median age 61 years; 41% women; 71% White • 99% received HFNC oxygen, NIV, or MV; 15% received MV. • 41% received MV during the study. • 31% to 37% crossed over to an alternative study treatment during the study. **Primary Outcome** • Composite of VTE or ATE events by hospital discharge or Day 28: 12% in full-dose anticoagulation arm vs. 6% in prophylactic anticoagulation arm (win ratio 1.95; 95% CI, 1.08–3.55; $P = 0.028$) **Secondary Outcome** • Composite of clinically evident VTE or ATE events by hospital discharge or Day 28: 10% in full-dose anticoagulation arm vs. 6% in prophylactic anticoagulation arm (win ratio 1.79; 95% CI, 0.92–3.47; $P = 0.087$) **Safety Outcomes** • No fatal bleeding events occurred. • Life-threatening bleeding events: 4 (2.1%) in full-dose anticoagulation arm vs. 1 (0.5%) in prophylactic anticoagulation arm ($P = 0.19$) • Moderate or severe bleeding events: 15 (7.9%) in full-dose anticoagulation arm vs. 1 (0.5%) in prophylactic anticoagulation arm ($P = 0.002$)	**Key Limitations** • Open-label study (adjudication committee members were blinded to the study arms). • Trial was stopped early because the decreasing number of ICU admissions for patients with COVID-19 made recruitment difficult. • There was an unequal crossover between the arms, with a greater crossover from the prophylactic anticoagulation arm to the full-dose anticoagulation arm. **Interpretation** • Among patients with COVID-19 who required ICU-level care, patients who received full-dose anticoagulation had fewer VTE or ATE events but no survival benefit compared to those who received prophylactic anticoagulation. • The prevalence of moderate or severe bleeding events was higher among patients who received full-dose anticoagulation than among those who received prophylactic anticoagulation.

Methods	Results	Limitations and Interpretation
REMAP-CAP/ACTIV-4a/ATTACC: Multiplatform, Open-Label RCT of Therapeutic Anticoagulation in Critically Ill, Hospitalized Patients With COVID-19 in 20 Countries[7]		

Key Inclusion Criteria
• Hospitalized with severe COVID-19 and receiving HFNC oxygen, NIV, MV, ECMO, vasopressors, or inotropes
• Hospitalized <72 hours (ACTIV-4a, ATTACC) or <14 days (REMAP-CAP)
Key Exclusion Criteria
• Hospital discharge expected in ≤72 hours
• Need for therapeutic anticoagulation or dual antiplatelet therapy
• High bleeding risk
Interventions
• Therapeutic UFH or LMWH for 14 days or until hospital discharge, whichever came first (n = 534)
• Usual care thromboprophylaxis (n = 564)
Primary Endpoint
• Number of organ support-free days by Day 21
Key Secondary Endpoints
• Survival to hospital discharge
• Any thrombosis
• Composite of major thrombotic events or death
• Bleeding events
	Participant Characteristics
	• Median age 60 years; 70% men; median BMI 30
	• 24% with chronic respiratory disease; 33% with DM; 10% with chronic kidney disease; 8% with severe CVD
	• 32% received HFNC oxygen; 38% received NIV; 29% received MV.
	• 18% on vasopressors; 82% on corticosteroids; 32% on RDV
	Primary Outcome
	• Median number of organ support-free days by Day 21: 4 in therapeutic arm vs. 5 in usual care arm (aOR 0.83; 95% CrI, 0.67–1.03; 99.9% posterior probability of futility; OR < 1.2)
	Secondary Outcomes
	• No difference between therapeutic and usual care arms in:
	  • Survival to hospital discharge: 63% vs. 65% (aOR 0.84; 95% CrI, 0.64–1.11)
	  • Thrombosis: 6% vs. 10%
	  • Composite of major thrombotic events or death: 41% in both arms
	  • Major bleeding events: 4% vs. 2% (aOR 1.48; 95% CrI, 0.75–3.04)
		Key Limitations
		• Open-label study
		• Dose of thromboprophylaxis varied in usual care arm (51% received intermediate dose; 2% received subtherapeutic dose; 5% received therapeutic dose).
		• Inclusion criteria for hospital LOS and ICU-level care differed across trials.
		• Trial stopped for futility.
		Interpretation
		• In patients who required ICU-level care, therapeutic heparin did not reduce the duration of organ support or mortality.
		• Although the differences were not significant, patients who received therapeutic anticoagulation had more bleeding events and fewer thrombotic events than patients who received usual care.

Methods	Results	Limitations and Interpretation
INSPIRATION: Open-Label RCT of Intermediate-Dose Versus Prophylactic-Dose Anticoagulation in Patients With COVID-19 in Intensive Care Units in Iran[8]		

Key Inclusion Criteria
• Admitted to ICU
• Hospitalized <7 days
Key Exclusion Criteria
• Life expectancy <24 hours
• Need for therapeutic anticoagulation
• Bleeding or high bleeding risk
Interventions
• Intermediate-dose anticoagulation: enoxaparin 1 mg/kg once daily (n = 276)
• Prophylactic-dose anticoagulation (n = 286)
Primary Endpoint
• Composite of adjudicated acute VTE, ATE, the need for ECMO, or all-cause mortality at 30 days
Key Secondary Endpoints
• All-cause mortality at 30 days
• VTE
• Bleeding events
	Participant Characteristics
	• Median age 62 years; 58% men; median BMI 27
	• 44% with HTN; 28% with DM; 14% with CAD
	• 32% received NIV; 20% received MV.
	• 23% on vasopressors; 93% on corticosteroids; 60% on RDV
	Primary Outcome
	• Composite of adjudicated acute VTE, ATE, the need for ECMO, or all-cause mortality at 30 days: 46% in intermediate-dose arm vs. 44% in prophylactic arm (OR 1.06; 95% CI, 0.76–1.48)
	Secondary Outcomes
	• No difference between intermediate-dose arm and prophylactic arm in:
	  • All-cause mortality at 30 days: 43% vs. 41%
	  • VTE: 3% in both arms
	  • Major bleeding events and clinically relevant, nonmajor bleeding events: 6.3% vs. 3.1% (OR 2.02; 95% CI, 0.89–4.61)
		Key Limitations
		• Open-label study
		• Not all patients received ICU-level care.
		Interpretation
		• Intermediate-dose anticoagulation did not significantly reduce the occurrence of VTE and ATE, the need for ECMO, or mortality.
		• Although the difference was not significant, patients who received intermediate-dose anticoagulation had more bleeding events than patients who received prophylactic-dose anticoagulation.

Methods	Results	Limitations and Interpretation
ANTICOVID: Open-Label RCT of Therapeutic-Dose Versus Intermediate-Dose Versus Prophylactic-Dose Anticoagulation in Patients With COVID-19 in Intensive Care Units in France[9]		
Key Inclusion Criterion • Hospitalized for <72 hours with hypoxemic COVID-19 pneumonia **Key Exclusion Criteria** • Weight <40 kg or >100 kg • Indication or contraindication for therapeutic anticoagulation • Bleeding or high bleeding risk **Interventions** • Therapeutic-dose anticoagulation: tinzaparin 175 IU/kg once daily or enoxaparin 100 IU/kg twice daily (n = 110) • Intermediate-dose anticoagulation: tinzaparin 7,000 IU once daily or enoxaparin 4,000 IU twice daily (n = 110) • Prophylactic-dose anticoagulation: tinzaparin 3,500 IU once daily or enoxaparin 4,000 IU once daily (n = 114) **Primary Endpoint** • Hierarchical outcome of all-cause mortality or time to clinical improvement of 2 points on a WHO scale by Day 28	**Participant Characteristics** • Mean age 58 years; 67% men; median BMI 27–28 • 31% with HTN; 18% with DM; 4% with CAD • 23% received conventional oxygen; 61% received HFNC oxygen; 7% received NIV; 10% received MV. • 92% on corticosteroids; 0.6% on RDV; 34% on tocilizumab; 3% on vasopressors **Primary Outcome** • No difference between arms for hierarchical outcome of all-cause mortality or time to clinical improvement by Day 28 **Secondary Outcomes** • Net clinical outcome by Day 28: 20.0% in therapeutic-dose arm vs. 16.4% in intermediate-dose arm vs. 29.8% in prophylactic-dose arm • Venous or arterial thrombosis: 5% in therapeutic-dose arm vs. 5% in intermediate-dose arm vs. 20% in prophylactic-dose arm • Major bleeding events: 4% in therapeutic-dose arm vs. 4% in intermediate-dose arm vs. 3% in prophylactic-dose arm	**Key Limitations** • Open-label study • Not all patients received ICU-level care. • Study excluded patients weighing >100 kg. • Tinzaparin is not available in the United States. **Interpretation** • The use of intermediate doses of anticoagulants improved the net clinical outcome by reducing the number of thrombosis events. • There was no difference between the arms in the occurrence of major bleeding events.

Methods	Results	Limitations and Interpretation
ACTIV-4B: Double-Blind RCT of Anticoagulant and Antiplatelet Therapy in Symptomatic, Nonhospitalized Patients With COVID-19 in the United States[10]		

Key Inclusion Criteria
• Aged 40–80 years
• Symptomatic SARS-CoV-2 infection
• CrCl >30 mL/min
• PLT >100,000 cells/μL
Key Exclusion Criteria
• Previously hospitalized with COVID-19
• Acute leukemia, recent major bleeding events, or indication or contraindication for anticoagulant or antiplatelet therapy
Interventions
• 558 of 657 randomized patients received study drugs.
• Aspirin 81 mg PO once daily for 45 days (n = 144)
• Prophylactic-dose anticoagulation: apixaban 2.5 mg PO twice daily for 45 days (n = 135)
• Therapeutic-dose anticoagulation: apixaban 5 mg PO twice daily for 45 days (n = 143)
• Placebo (n = 136)
Primary Endpoint
• Composite of all-cause mortality, symptomatic VTE, ATE, MI, stroke, or hospitalization for cardiovascular or pulmonary cause at 45 days
Key Secondary and Safety Endpoints
• Component events of primary endpoint
• Major bleeding
	Participant Characteristics
	• Listed characteristics are for all 657 randomized patients.
	• Median age 54 years; 59% women; median BMI 30; 13% Black, 28% Hispanic
	• 18% with DM; 20% with a history of smoking; 35% with HTN
	Primary Outcome
	• Composite of all-cause mortality, symptomatic VTE, ATE, MI, stroke, or hospitalization at 45 days: 1 (0.7%) in aspirin arm vs. 1 (0.7%) in apixaban 2.5 mg arm vs. 2 (1.4%) in apixaban 5 mg arm vs. 1 (0.7%) in placebo arm
	• Risk differences compared with placebo:
	  • 0.0% (95% CI, not calculable) in aspirin arm
	  • 0.7% (95% CI, -2.1% to 4.1%) in 2.5 mg apixaban arm
	  • 1.4% (95% CI, -1.5% to 5.0%) in 5 mg apixaban arm
	• Cumulative incidence of primary outcomes did not significantly differ across treatment arms (log-rank P = 0.78).
	Secondary Outcome
	• No differences between all treatment arms and placebo arm in occurrence of individual components of the primary endpoint
	Safety Outcome
	• No major bleeding events occurred.
		Key Limitation
		• Initial target sample size was 7,000 patients, but trial was terminated after enrolling only 9% of target because of a low event rate.
		Interpretation
		• Among symptomatic outpatients with COVID-19 who were clinically stable, treatment with aspirin or a therapeutic or prophylactic dose of apixaban did not reduce the risk of death, symptomatic VTE or ATE, or hospitalization for cardiovascular or pulmonary causes compared to placebo.

Methods	Results	Limitations and Interpretation
OVID: Open-Label RCT of Low-Molecular-Weight Heparin for Thromboprophylaxis in Symptomatic, Nonhospitalized Patients With COVID-19 in Germany and Switzerland[11]		
Key Inclusion Criteria • Aged ≥50 years • Positive SARS-CoV-2 test result within past 5 days • Respiratory symptoms or temperature ≥37.5 °C **Key Exclusion Criteria** • Severe renal or hepatic dysfunction • Severe anemia or recent major bleeding events • Receiving dual antiplatelet therapy **Interventions** • Enoxaparin 40 mg SUBQ once daily for 14 days (n = 234) • SOC (n = 238) **Primary Endpoint** • Composite of any untoward hospitalization or all-cause death by Day 30 **Key Secondary Endpoint** • Composite of major arterial and venous cardiovascular events by Day 30 • Bleeding events	**Participant Characteristics** • Median age 57 years; 46% women; 96% White • Median of 3 days from COVID-19 diagnosis to randomization • 24% with HTN; 8% with DM; 5% with CVD • 9.5% received ≥1 COVID-19 vaccine doses. **Primary Outcome** • Composite of any untoward hospitalization or all-cause death by Day 30: 8 (3%) in enoxaparin arm vs. 8 (3%) in SOC arm (adjusted relative risk 0.98; 95% CI, 0.37–2.56; $P = 0.96$) **Secondary Outcomes** • Composite of major arterial and venous cardiovascular events by Day 30: 2 (1%) in enoxaparin arm vs. 4 (2%) in SOC arm (relative risk 0.51; 95% CI, 0.09–2.74) • No major or clinically relevant, nonmajor bleeding events occurred.	**Key Limitations** • Open-label study • Trial terminated early due to a low probability that enoxaparin would be superior to the standard of care for the primary outcome. **Interpretation** • Thromboprophylaxis with enoxaparin did not reduce the risk of hospitalization or death among nonhospitalized, symptomatic patients with COVID-19.

Methods	Results	Limitations and Interpretation
ETHIC: Open-Label RCT of Low-Molecular-Weight Heparin for Thromboprophylaxis in Symptomatic Outpatients With COVID-19 in Belgium, Brazil, India, South Africa, Spain, and the United Kingdom[12]		
Key Inclusion Criteria • Aged ≥30 years • RT-PCR-confirmed SARS-CoV-2 infection, with symptoms for ≤9 days • ≥1 risk factors for severe disease **Key Exclusion Criteria** • Receipt of a COVID-19 vaccine • eGFR <30 mL/min • Receiving anticoagulant or antiplatelet therapy, except low-dose aspirin **Interventions** • Enoxaparin 40 mg SUBQ once daily (for patients weighing <100 kg) or enoxaparin 40 mg SUBQ twice daily (for patients weighing ≥100 kg), self-administered for 21 days (n = 105) • SOC (n = 114) **Primary Endpoint** • Composite of all-cause hospitalization or all-cause mortality by Day 21 **Key Secondary Endpoints** • VTE by Day 90 • Bleeding events by Day 50	**Participant Characteristics** • Median age 59 years; 56% men • Median of 5 days from first symptom to randomization **Primary Outcomes** • Composite of all-cause hospitalization or all-cause mortality by Day 21: 12 (11%) in enoxaparin arm vs. 12 (11%) in SOC arm (HR 1.09; 95% CI, 0.49–2.43; P = 0.83) • Patients who required hospitalization: 12 in enoxaparin arm vs. 12 in SOC arm • Hospitalized patients who required acute medical care or ICU admission: 4 in enoxaparin arm vs. 0 in SOC arm **Secondary Outcomes** • VTE by Day 90: 1 (1%) in enoxaparin arm vs. 2 (2%) in SOC arm • Bleeding events by Day 50: 2 (2%) in enoxaparin arm vs. 2 (2%) in SOC arm	**Key Limitations** • Open-label study • Study terminated early because of low event rate and lack of efficacy. **Interpretation** • This study demonstrated no benefit of prophylaxis with LMWH in outpatients with COVID-19 who were at risk of progressing to severe disease.

Methods	Results	Limitations and Interpretation
ACTIV-4C: Double-Blind RCT of 30 Days of Apixaban After Hospital Discharge in Patients With COVID-19 in the United States[13]		
Key Inclusion Criteria • Hospitalized >48 hours with confirmed SARS-CoV-2 infection within 2 weeks of admission • PLT >50,000 cells/μL and Hgb >8 g/dL **Key Exclusion Criteria** • Need for therapeutic or prophylactic anticoagulation at hospital discharge • Ischemic stroke, intracranial bleed, or neurosurgery within 3 months • Bleeding events within past 30 days • Major surgery within 14 days • Inherited or active acquired bleeding disorder **Interventions** • Apixaban 2.5 mg PO twice daily for 30 days, starting at hospital discharge (n = 610) • Placebo (n = 607) **Primary Endpoint** • Composite of death, ATE, or VTE by Day 30 **Key Safety Endpoint** • Bleeding events	**Participant Characteristics** • Median age 54 years; 50% men; 27% Black, 17% Hispanic • 15% on antiplatelet therapy • At hospital discharge, 16% were prescribed antiplatelet therapy; 93% received aspirin. **Primary Outcome** • Composite of death, ATE, or VTE by Day 30: 13 (2.1%) in apixaban arm vs. 14 (2.3%) in placebo arm (relative risk 0.92; 95% CI, 0.44–1.95; $P = 0.85$) **Safety Outcomes** • Major bleeding events: 2 (0.4%) in apixaban arm vs. 1 (0.2%) in placebo arm (relative risk 2.00; 95% CI, 0.18–22.03) • Clinically relevant, nonmajor bleeding events: 3 (0.6%) in apixaban arm vs. 6 (1.1%) in placebo arm (relative risk 0.50; 95% CI, 0.13–1.99)	**Key Limitation** • Trial was terminated early due to a low event rate and because the decreasing number of hospitalizations for people with COVID-19 made recruitment difficult. **Interpretation** • Incidence of death or thromboembolism was low in this cohort of patients. • Because the trial was terminated early, the results were imprecise, and the study was inconclusive.

Methods	Results	Limitations and Interpretation
MICHELLE: Open-Label RCT of Using Rivaroxaban After Hospital Discharge in Patients With COVID-19 Who Were at High Risk of Venous Thromboembolism in Brazil[14]		
Key Inclusion Criteria • Hospitalized for ≥3 days with confirmed SARS-CoV-2 infection • Increased risk of VTE, defined as an IMPROVE VTE score at hospital discharge of >4 or 2–3 with D-dimer >500 ng/mL **Key Exclusion Criterion** • Suspicion or confirmation of a thrombotic event **Interventions** • Rivaroxaban 10 mg PO once daily for 35 days, starting at hospital discharge (n = 159) • No anticoagulation (n = 159) **Primary Endpoint** • Composite of symptomatic or fatal VTE, asymptomatic VTE on bilateral lower-limb venous ultrasound and CTPA, symptomatic ATE, or cardiovascular death by Day 35 **Key Secondary Endpoints** • Symptomatic or fatal VTE • Composite of symptomatic VTE, MI, non-hemorrhagic stroke, or cardiovascular death **Key Safety Endpoint** • Bleeding events	**Participant Characteristics** • Median age 57 years; 60% men • While hospitalized, 86% received thromboprophylaxis with enoxaparin, 14% received unfractionated heparin, and 5% received antiplatelet therapy. **Primary Outcome** • Primary composite outcome by Day 35: 5 (3%) in rivaroxaban arm vs. 15 (9%) in no anticoagulation arm (relative risk 0.33; 95% CI, 0.12–0.90; $P = 0.03$) • Difference driven mainly by incidence of PE (2 in rivaroxaban arm vs. 10 in no anticoagulation arm). **Secondary Outcomes** • Symptomatic or fatal VTE: 1 (0.6%) in rivaroxaban arm vs. 8 (5.0%) in no anticoagulation arm (relative risk 0.13; 95% CI, 0.02–0.99; $P = 0.049$) • Composite of symptomatic VTE, MI, non-hemorrhagic stroke, or cardiovascular death: 1 (0.6%) in rivaroxaban arm vs. 9 (5.7%) in no anticoagulation arm (relative risk 0.11; 95% CI, 0.01–0.87; $P = 0.036$) **Safety Outcome** • No major bleeding events occurred.	**Key Limitations** • Open-label study with no placebo • Not all patients had the protocol-specified CTPA or Doppler ultrasound during the study. However, a higher number of imaging evaluations occurred among the patients in the rivaroxaban arm. **Interpretation** • In patients who were at high risk of VTE, the use of thromboprophylaxis with rivaroxaban 10 mg PO once daily for 35 days improved clinical outcomes when compared with no anticoagulation.

Key: ATE = arterial thromboembolism; BARC = Bleeding Academic Research Consortium; BMI = body mass index; CAD = coronary artery disease; CrCl = creatinine clearance; CTPA = computed tomography pulmonary angiogram; CVD = cardiovascular disease; DEX = dexamethasone; DM = diabetes mellitus; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HFNC = high-flow nasal cannula; Hgb = hemoglobin; HIT = heparin-induced thrombocytopenia; HTN = hypertension; ICU = intensive care unit; IMPROVE = International Medical Prevention Registry on Venous Thromboembolism; ISTH = International Society on Thrombosis and Haemostasis; LMWH = low-molecular-weight heparin; LOS = length of stay; MI = myocardial infarction; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PE = pulmonary embolism; PLT = platelet count; PO = oral; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SOC = standard of care; SpO_2 = oxygen saturation; SUBQ = subcutaneous; UFH = unfractionated heparin; ULN = upper limit of normal; VTE = venous thromboembolism; WHO = World Health Organization

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