Table 6b. Antiplatelet Therapy: Selected Clinical Trial Data

Last Updated: February 29, 2024

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

Methods	Results	Limitations and Interpretation
ACTIV-4a: Open-Label, Adaptive RCT of Adding a P2Y12 Inhibitor to Anticoagulant Therapy in Noncritically Ill Hospitalized Patients With COVID-19 in Brazil, Italy, Spain, and the United States[1]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• Any 1 of the following:
  • D-dimer level ≥2 times ULN
  • Aged 60–84 years
  • Aged <60 years with oxygen requirement >2 L/min, HTN, DM, eGFR <60 mL/min, CVD, or BMI ≥35
Key Exclusion Criteria
• Required HFNC oxygen ≥20 L/min, NIV, MV, ECMO, vasopressors, or inotropes
• ≥72 hours since hospital admission
Interventions
• Therapeutic dose of heparin plus P2Y12 inhibitor for 14 days or until hospital discharge, whichever came first (n = 293)
• Therapeutic dose of heparin (usual care arm; n = 269)
Primary Endpoints
• Number of organ support-free days by Day 21
• Major bleeding events by Day 28
Key Secondary Endpoint
• Composite of major thrombotic events or death by Day 28
	Participant Characteristics
	• Mean age 53 years; 42% women; 62% White
	• HTN: 43% in P2Y12 inhibitor arm vs. 55% in usual care arm
	• 65% received glucocorticoids; 52% received RDV; 3% received IL-6 inhibitors; 14% received aspirin.
	• Median duration of P2Y12 inhibitor treatment was 6 days.
	  • 63% received ticagrelor; 37% received clopidogrel.
	Primary Outcomes
	• Median number of organ support-free days by Day 21: 21 in both arms (aOR 0.83; 95% CrI, 0.55–1.25; posterior probability of futility 96%)
	• Major bleeding events by Day 28: 2.0% in P2Y12 inhibitor arm vs. 0.7% in usual care arm (aOR 3.31; 95% CI, 0.64–17.2; $P = 0.15$)
	Secondary Outcome
	• Composite of major thrombotic events or death by Day 28: 6.1% in P2Y12 inhibitor arm vs. 4.5% in usual care arm (aOR 1.42; 95% CI, 0.64–3.13)
		Key Limitations
		• Open-label study
		• Study was stopped early for futility.
		• Different P2Y12 inhibitors were used.
		• Median duration of P2Y12 inhibitor treatment was 6 days, which may not be sufficient to observe effects.
		Interpretation
		• Among hospitalized patients with COVID-19 who were not critically ill, adding a P2Y12 inhibitor to a therapeutic dose of heparin did not increase the number of organ support-free days.
		• Major bleeding events occurred infrequently during the study. The number of patients who experienced a major bleeding event was not significantly different between the arms.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Aspirin in Hospitalized Patients With COVID-19 in Indonesia, Nepal, and the United Kingdom[2]		

Key Inclusion Criterion
• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criteria
• Hypersensitivity to aspirin
• Recent history of major bleeding events
• Currently receiving aspirin or another antiplatelet treatment
Interventions
• Aspirin 150 mg once daily until hospital discharge (n = 7,351)
• SOC alone (n = 7,541)
Primary Endpoint
• All-cause mortality at 28 days
Key Secondary Endpoints
• Composite of progression to MV or death at 28 days
• Major bleeding events at 28 days
• Thrombotic events at 28 days
	Participant Characteristics
	• Mean age 59 years; 62% men; 75% White
	• 97% had laboratory-confirmed SARS-CoV-2 infection
	• At baseline:
	  • 5% on MV
	  • 28% on NIV
	  • 34% received intermediate- or therapeutic-dose LMWH.
	  • 60% received standard-dose LMWH.
	  • 7% received no thromboprophylaxis.
	• 94% received corticosteroids; 26% received RDV; 13% received tocilizumab; 6% received baricitinib.
	Primary Outcome
	• All-cause mortality at 28 days: 17% in both arms (rate ratio 0.96; 95% CI, 0.89–1.04; $P = 0.35$)
	Secondary Outcomes
	• Composite of progression to MV or death at 28 days: 21% in aspirin arm vs. 22% in SOC arm (risk ratio 0.96; 95% CI, 0.90–1.03)
	• Major bleeding events at 28 days: 1.6% in aspirin arm vs. 1.0% in SOC arm ($P = 0.0028$)
	• Thrombotic events at 28 days: 4.6% in aspirin arm vs. 5.3% in SOC arm ($P = 0.07$)
		Key Limitation
		• Because of the open-label design, reporting of major bleeding and thrombotic events may have been influenced by the treatment allocation.
		Interpretation
		• In hospitalized patients with COVID-19, the use of aspirin was not associated with reductions in 28-day mortality or the risk of progressing to MV or death.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive RCT of Antiplatelet Therapy in Critically Ill Patients With COVID-19 in 8 Countries in Europe and Asia[3]		

Key Inclusion Criteria
• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection
• Within 48 hours of ICU admission
Key Exclusion Criteria
• Bleeding risk sufficient to contraindicate antiplatelet therapy
• CrCl <30 mL/min
• Receiving antiplatelet therapy or NSAIDs
Interventions
• 1 of the following plus anticoagulation for 14 days or until hospital discharge, whichever came first:
  • Aspirin 75–100 mg once daily (n = 565)
  • P2Y12 inhibitor (n = 455)
  • No antiplatelet therapy (control arm; n = 529)
Primary Endpoint
• Number of organ support-free days by Day 21
Key Secondary Endpoints
• Survival to hospital discharge
• Survival to Day 90
• Major bleeding events by Day 14
	Participant Characteristics
	• Mean age 57 years; 34% women; 77% White
	• At baseline, 98% were receiving LMWH:
	  • 19% received low-dose LMWH.
	  • 59% received intermediate-dose LMWH.
	  • 12% received therapeutic-dose LMWH.
	• 98% received steroids; 21% received RDV; 44% received tocilizumab; 11% received sarilumab.
	• In P2Y12 inhibitor arm, 88.5% received clopidogrel, 1.3% received ticagrelor, 1.3% received prasugrel, and 8.8% received an unknown P2Y12 inhibitor.
	Primary Outcome
	• Data from aspirin and P2Y12 inhibitor arms were pooled and reported as "pooled antiplatelet arm" in final analysis:
	  • Median number of organ support-free days by Day 21: 7 in pooled antiplatelet arm vs. 7 in control arm (aOR 1.02; 95% CrI, 0.86–1.23; posterior probability of futility 96%)
	Secondary Outcomes
	• Survival to hospital discharge: 71.5% in pooled antiplatelet arm vs. 67.9% in control arm (median-adjusted OR 1.27; 95% CrI, 0.99–1.62; adjusted absolute difference 5%; 95% CrI, -0.2% to 9.5%; 97% posterior probability of efficacy)
	• Survival to Day 90: 72% in pooled antiplatelet arm vs. 68% in control arm (HR with pooled antiplatelets 1.22; 95% CrI, 1.06–1.40; 99.7% posterior probability of efficacy)
	• Major bleeding events by Day 14: 2.1% in pooled antiplatelet arm vs. 0.4% in control arm (aOR 2.97; 95% CrI, 1.23–8.28; posterior probability of harm 99.4%)
		Key Limitations
		• Open-label study
		• Different P2Y12 inhibitors were used.
		• Trial was stopped for futility. Because equivalence for aspirin and P2Y12 inhibitor arms was reached, these arms were pooled for analyses.
		Interpretation
		• In critically ill patients with COVID-19, the use of aspirin or a P2Y12 inhibitor did not reduce the number of organ support-free days or in-hospital mortality.
		• Patients in the pooled antiplatelet arm had more major bleeding events than those in the control arm, but they had improved survival over 90 days.

Methods	Results	Limitations and Interpretation
COVID-PACT: Open-Label RCT of Clopidogrel in Adults With COVID-19 Who Were Receiving Intensive Care Unit-Level Care in the United States[4]		
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 a therapeutic dose of anticoagulation or dual antiplatelet therapy • High risk of bleeding • History of HIT • Ischemic stroke within 2 weeks **Interventions** • Clopidogrel 300 mg at randomization, then clopidogrel 75 mg once daily until hospital discharge or Day 28, whichever came first (n = 152) • No clopidogrel therapy (n = 140) • Some patients were also randomized to receive a therapeutic or prophylactic dose of anticoagulation (n = 290) **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 events or acute limb ischemia, and clinically silent DVT. **Secondary Endpoint** • Composite of clinically evident VTE or ATE events by hospital discharge or Day 28 **Safety Endpoints** • Fatal or life-threatening bleeding events • Moderate or severe bleeding events	**Participant Characteristics** • Median age 58 years; 41% women; 71% White • At baseline, 99% on HFNC oxygen, NIV, or MV; 15% on MV • 37% required MV during the study. **Primary Outcome** • Composite of VTE or ATE events by hospital discharge or Day 28: 10% in both arms (win ratio 1.04; 95% CI, 0.54–2.01; *P* = 0.90) **Secondary Outcome** • Composite of clinically evident VTE or ATE events by hospital discharge or Day 28: 7% in clopidogrel arm vs. 9% in no clopidogrel arm (win ratio 0.79; 95% CI, 0.38–1.65; *P* = 0.53) **Safety Outcomes** • Fatal or life-threatening bleeding events: 1.3% in clopidogrel arm vs. 1.4% in no clopidogrel arm (*P* = 1.00) • Moderate or severe bleeding events: 4.0% in clopidogrel arm vs. 6.4% in no clopidogrel arm (*P* = 0.83)	**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. • 31% discontinued clopidogrel. **Interpretation** • In patients with COVID-19 who required ICU-level care, clopidogrel did not reduce the incidence of thrombotic complications.

Key: ATE = arterial thromboembolism; BMI = body mass index; CrCl = creatinine clearance; CVD = cardiovascular disease; DM = diabetes mellitus; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HFNC = high-flow nasal cannula; HIT = heparin-induced thrombocytopenia; HTN = hypertension; ICU = intensive care unit; IL = interleukin; LMWH = low-molecular-weight heparin; MI = myocardial infarction; MV = mechanical ventilation; NIV = noninvasive ventilation; NSAID = nonsteroidal anti-inflammatory drug; the Panel = the COVID-19 Treatment Guidelines Panel; PE = pulmonary embolism; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; ULN = upper limit of normal; VTE = venous thromboembolism

References

1. Berger JS, Kornblith LZ, Gong MN, et al. Effect of P2Y12 inhibitors on survival free of organ support among non-critically ill hospitalized patients with COVID-19: a randomized clinical trial. *JAMA*. 2022;327(3):227-236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35040887.
2. RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2022;399(10320):143-151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34800427.
3. REMAP-CAP Writing Committee for the REMAP-CAP Investigators. Effect of antiplatelet therapy on survival and organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2022;327(13):1247-1259. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35315874.
4. Bohula EA, Berg DD, Lopes MS, et al. Anticoagulation and antiplatelet therapy for prevention of venous and arterial thrombotic events in critically ill patients with COVID-19: COVID-PACT. *Circulation*. 2022;146(18):1344-1356. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36036760.