Improving End Organ Dysfunction and Survival with Antiplatelet Agents in Community Acquired Pneumonia

By:

Sylvain Lother

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Department of Community Health Sciences
Rady Faculty of Health Sciences
University of Manitoba

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ABSTRACT

Background: Community acquired pneumonia (CAP) is a life-threatening lung infection and the most common reason for hospital admission. Both COVID-19 and non-COVID-19 CAP trigger inflammatory and thrombotic host responses driving morbidity and mortality. In non-critically ill patients hospitalized for COVID-19, therapeutic-dose heparin improves survival and reduces intensive care unit (ICU)-level organ support. Antiplatelet agents may also favorably modulate host responses; however, their role in COVID-19 and non-COVID-19 CAP remains uncertain.

Objectives: The overall objective was to evaluate the treatment effects and safety of antiplatelet agents and their interactions with therapeutic-dose heparin in CAP. Specifically, we aimed to meta-analyze the effect of antiplatelet agents in non-COVID-19 CAP, and to evaluate the effect of combination antiplatelet agents with therapeutic-dose heparin in COVID-19 CAP.

Methods: We conducted a systematic review/meta-analysis of observational studies and randomized controlled trials (RCTs) of hospitalized patients with non-COVID-19 CAP evaluating the effect of antiplatelet agents (ASA or P2Y12 inhibitors) on mortality. We conducted a secondary analysis of the multiplatform trial (mpRCT) to evaluate the effect of combination antiplatelet agents with therapeutic-dose heparin compared to therapeutic-dose heparin alone in COVID-19.

Results: We meta-analyzed 13 observational studies and 2 RCTs in our systematic review. In observational studies reporting hazard ratio (HR), antiplatelet agents were associated with lower mortality (HR 0.65, 95% CI 0.46-0.91; I^2 85%; 4 studies, 91,430 patients). In studies reporting adjusted odds ratio (aOR), antiplatelet agents were associated with reduced odds of mortality (aOR 0.67, 95% CI 0.45 – 1.00, I^2 0%; 2 studies, 24,899 patients). Among RCTs there was a non-significant association with mortality (risk ratio 0.66, 95% CI 0.20 – 2.25; I^2 54%, 2 studies, 225 patients). In our secondary analysis of the mpRCT, 1,021 patients hospitalized with COVID-19 received therapeutic-dose heparin, of which 19% concurrently received an antiplatelet agent. Combination treatment was not associated with an improvement in survival without the need for organ support (OR 1.07, 95% CI 0.71 – 1.64).

Conclusions: Antiplatelet agents may be associated with reduced mortality in hospitalized patients with non-COVID-19 CAP, but the certainty of the evidence was low. Exposure to combination antiplatelet and therapeutic-dose heparin in COVID-19 did not improve outcomes. This thesis has provided foundational work to inform the design of a future RCT of antiplatelet agents in CAP.

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MANUSCRIPTS

My MSc thesis is written in the grouped manuscript style and consists of the following collection of published and completed manuscripts:

1. Lother SA, Tennenhouse LG, Rabbani R, Abou-Setta AM, Askin N, Turgeon AF, Murthy S, Houston BL, Houston DS, Mendelson AA, Rush B, Rimmer E, Marshall JC, Shaw SY, Lawler PR, Keynan Y, Zarychanski R. The effect of anti-platelet agents on end organ dysfunction and mortality in community acquired pneumonia: A protocol for a systematic review and meta-analysis. *medRxiv*. Apr 2024: 2024.04.16.24305938
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2. Lother SA, Tennenhouse LG, Rabbani R, Abou-Setta AM, Askin N, Turgeon AF, Murthy S, Houston BL, Houston DS, Mendelson AA, Paul JD, Farkouh ME, Hasmatali J, Rush B, Nkosi J, Goligher EC, Rimmer E, Marshall JC, Shaw SY, Lawler PR, Keynan Y, Zarychanski R. The association of antiplatelet agents with mortality among patients with non-COVID-19 community acquired pneumonia: A systematic review and meta-analysis. *Res Pract Thromb Haemost*. Jul 2024; S2475-0379(24)00221-8
   DOI: https://doi.org/10.1016/j.rpth.2024.102526

3. Lother SA, Teng W, Ayilara O, Houston BL, Turgeon AF, Murthy S, Houston DS, Mendelson AA, Farkouh ME, Rush B, Goligher EC, Shaw S, Lawler PR, Keynan Y, Zarychanski R. Therapeutic-dose heparin in combination with antiplatelet agents in non-critically ill patients hospitalized for COVID-19: A secondary analysis of the multiplatform randomized controlled trial (mpRCT). *Pending submission*.

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ABBREVIATIONS

ACTIV-4a	A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19
ASA	acetylsalicylic acid
ATTACC	AntiThrombotic Therapy to Ameliorate Complications of COVID-19
ATTACC-CAP	AntiThrombotic Therapy to Ameliorate Clinical Complications in Community Acquired Pneumonia
CAP	community acquired pneumonia
CI	confidence interval
COVID-19	COronaVirus Disease of 2019
COX-1	cyclooxygenase-1
CrI	credible interval
DAMP	damage-associated molecular patterns
DVT	deep venous thrombosis
HFNO	high flow nasal oxygen
HR	hazard ratio
ICU	intensive care unit
IL	interleukin
IMV	invasive mechanical ventilation
IPTW	inverse probability of treatment weighting
MI	myocardial infarction
mpRCT	multiplatform randomized controlled trial
NET	neutrophil extracellular traps
NF	nuclear factor
NIV	non-invasive ventilation
OR	odds ratio
p-y	person-years
PAMP	pathogen-associated molecular patterns
PE	pulmonary embolism
RCT	randomized controlled trial
RECOVERY	Randomized Evaluation of COVID-19 Therapy
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive, Platform trial in Community Acquired Pneumonia
RR	relative risk
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus-2
TNF	tumour necrosis factor
VTE	venous thromboembolism
US	United States
USD	United States Dollar

1.0 BACKGROUND

1.1 Introduction

Community acquired pneumonia (CAP) is a life-threatening lung infection typically caused by bacteria and viruses, and is the most common cause of infection-related mortality globally.[1,2] Infectious pathogens cause local tissue injury in pulmonary alveoli, causing local and systemic inflammatory responses and activation of thrombotic host mechanisms. Organ dysfunction can result from a dysregulated host inflammatory and thrombotic response, driven by micro- and macro-vascular thrombosis and tissue injury.[3,4] Antimicrobials are administered to reduce or eliminate the driver; however, effective therapies that modulate cascading host responses to infection are lacking. Antiplatelet medications have pleotropic effects that biologically attenuate thrombotic and inflammatory host responses, however their potential impact in patients hospitalized with CAP remains uncertain.

1.2 Impact of CAP

CAP is a leading cause of hospitalization and mortality globally. The incidence of hospitalization for CAP ranges, by country, from 18-290 per 10,000 person-years (p-y).[1] In Canada, CAP was the 3rd most common reason for hospitalization in 2019 (69,403 hospitalizations),[5] with an incidence higher than most other high-income countries (214-280 cases per 10,000 p-y).[6] In the United States, CAP is the 2nd most common reason for hospitalization, accounting for 1.1-1.5 million admissions and up to $40 billion USD annually.[7,8] CAP incidence increases with age, affecting 2% of all US citizens aged ≥ 65 each year.[8]

Morbidity and mortality for patients hospitalized with CAP are high; overall mortality at 30-days is 12-13%,[7,9] and at 6 months is 23%.[7] Between 6-21% require Intensive Care Unit (ICU) admission,[10,11] with a mortality risk of 37% among ICU patients.[12] In Canada, CAP accounted for 5,931 deaths in 2020.[13] In the US, CAP accounts for 60,000 – 100,000 deaths per year.[7,14] Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2-2) is now a predominant viral pathogen in CAP, significantly increasing the global burden of pneumonia. Globally, respiratory infections are the most fatal communicable disease, and the 4th most common cause of death overall, accounting for 2.6 million deaths annually.[15]

1.3 Inflammation, thrombosis, and platelet activation in CAP

The pathophysiology of organ dysfunction in CAP involves endothelial injury, endothelial dysfunction, and activation of the inflammatory and coagulation pathways, leading to tissue injury. Infectious pathogens may directly infect endothelial cells, leading to cytopathic effects within the vascular endothelium, activating inflammation within the circulation, activating platelets and triggering coagulation cascades, increasing vascular permeability, affecting vasomotor function, and allowing immune cell infiltration of end organs.[16] The innate immune system is also activated in recognition of pathogens and tissue injury, driving local and systemic inflammation and hypercoagulability. Tissue injury in response to thrombosis leads to further activation of inflammation and hypercoagulability, amplifying the response. This bidirectional interaction between inflammation and coagulation is termed immunothrombosis. Endothelial dysfunction and immunothrombotic mechanisms persist for days to months after infection.[17,18]

The immunothrombosis cascade is triggered by circulating monocytes recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) which leads to expression and delivery of soluble tissue factor in the systemic circulation, initiating coagulation. Neutrophil extracellular traps (NETs) are produced and can directly activate coagulation pathways, attract and activate platelets, and inactivate endogenous anticoagulants, promoting a hypercoagulable milieu. Lastly, the complement system activates platelets directly, and platelets activate tissue factor, further amplifying hypercoagulability.[3]

Excessive inflammation and coagulation contribute to organ dysfunction due to micro- and macro-vascular thrombosis. The risk of any vascular thrombosis is elevated in CAP and occurs in ~11% of patients at 30-days.[19-21] An increased risk of venous thromboembolism (VTE) was seen at the onset of the COVID-19 pandemic,[22,23] and the incidence of symptomatic VTE in COVID-19 and CAP is comparable (2.0% vs. 3.6%, respectively), and higher in mechanically ventilated patients.[24] Additionally, influenza may be associated with an even greater risk of arterial thrombosis compared with COVID-19 (7.5% vs. 4.4%, respectively).[19]

Cardiovascular events driven by vascular immunothrombosis complicates CAP in up to a third of hospitalizations.[7,21,25] Inflammatory cells contained within coronary plaques are activated by circulating inflammatory cytokines (interleukins (IL) 1, 6, 8, and tumor necrosis factor α).

Inflammatory activity within plaques promote oxidative bursts and up-regulate metalloproteinases and peptidases which contribute to plaque destabilization and myocardial infarction (MI).[25] Viral infections lead to a 3-6 fold increase in MI in the week after hospitalization.[26] Pneumococcal pneumonia is associated with a 7-8% incidence rate of MI during hospitalization.[25] This risk persists, with a 48-fold increase in MI in the first two weeks after hospitalization, compared to the year before CAP. These cardiovascular events are associated with a greater than 3-fold increase in mortality.[21] Although patients with CAP are at increased risk for MI, no proven treatments prevent this outcome.

The physiologic response to excessive inflammation and thrombotic mechanisms after a primary infection leads to longer term host vulnerabilities to secondary infections. For instance, in response to a primary influenza viral pneumonia, attenuation of the immunopathologic responses is achieved by modulation of host toll-like receptors within alveolar macrophages, reducing their responsiveness to pulmonary pathogens, leading to reduced neutrophil recruitment, reduced pathogen clearance, and increased risk of secondary bacterial pneumonia. Additionally, regulatory T-cells producing immunosuppressive cytokines (IL-10) that are activated after primary infection can attenuate the response to a secondary infection.[27] Maladaptive host immunothrombotic responses to a pulmonary infection contributes to short- and longer-term morbidity and mortality.

1.4 Knowledge gaps

1.4.1 Antiplatelets in CAP

Antiplatelets work primarily by preventing platelet aggregation. Acetylsalicylic acid (ASA) is the most common, familiar, inexpensive, and widely available oral antiplatelet medication with pleotropic effects that may benefit patients with CAP. ASA exhibits antiplatelet activity by irreversibly acetylating cyclooxygenase-1 (COX-1) and reducing platelet activation through the inhibition of thromboxane A2. In addition to inhibiting platelet activation, ASA reduces pro-inflammatory prostaglandin production,[28] inhibits neutrophil activation and responses,[29] reduces inducible nitric oxide synthases,[30] and inhibits the activation of nuclear factor (NF)-kappa B, a transcription factor that induces production of inflammatory cytokines (IL-1, IL-6, TNF).[31] Relaxation of vascular endothelium through the inhibition of thromboxane A2 also occurs with ASA which mitigates vasoconstriction from platelet aggregation.[32] These mechanisms hold promise in blunting host immunothrombotic responses to infection.

The role of antiplatelets in CAP remains uncertain. In a small randomized control trial (RCT), ASA was shown to reduce MI and cardiovascular death in patients admitted to hospital with CAP.[33] Several retrospective and prospective cohort studies suggest potential benefit with antiplatelet exposure; however, inconsistent results and variability in studied patient populations means that the effect of antiplatelet agents in hospitalized patients with CAP remains uncertain.[34-36] Due to the heterogeneity of CAP, it is likely heterogenous treatment effects may exist according to patient or pathogen characteristics. Such effects have not yet been explored.

1.4.2 Antithrombotics and antiplatelets in COVID-19

CAP from COVID-19 served to illustrate the importance of modulating the host response to infection. Dexamethasone, tocilizumab, and therapeutic-dose anticoagulation with heparin - therapies that modulate the inflammatory and thrombotic pathways - have all been shown to improve outcomes in hospitalized patients with COVID-19, with differential treatment effects across various subgroups.[22,37-40] In the multiplatform randomized control trial (mpRCT) in COVID-19 pneumonia, therapeutic-dose anticoagulation with heparin reduced organ dysfunction and improved survival for those with moderate illness before the onset of organ failure.[22] A similar treatment effect was shown in other trials and is now recommended in treatment guidelines.[41,42]

The role of antiplatelets in COVID-19 is less certain. ASA demonstrated mixed effects in clinical trials, some showing benefit and others showing no significant effect.[43-45] Further analyses suggests that ASA may benefit individuals at longer follow up duration (180-day).[46] How ASA modifies the effectiveness and safety of therapeutic-dose anticoagulation in COVID-19 CAP has not yet been ascertained. Although combination anticoagulation and antiplatelets have demonstrated benefit in other hyper-inflammatory and thrombotic conditions, including myocardial infarction and stroke, their effects in combination for COVID-19 must be explored and balanced with an excess potential risk of bleeding.[47,48] Whether antiplatelets modify the effect of therapeutic-dose heparin in COVID-19 remains uncertain.

1.4.3. Opportunity for innovation in Manitoba

Advancing the lessons learned through COVID-19, our research group is now investigating the effect of therapeutic-dose heparin in non-critically ill patients hospitalized for non-COVID-19

CAP in the AntiThrombotic Therapy to Ameliorate Clinical Complications in Community Acquired Pneumonia (ATTACC-CAP) trial. This is a large international adaptive trial that is co-led by local principal investigators in Manitoba. Within an international network, this trial provides an opportunity to study other important host-directed interventions in a platform trial infrastructure. By addressing knowledge gaps outlined in this thesis, this thesis will inform the possible addition of a randomized comparative antiplatelet intervention within the trial.

2.0 THESIS HYPOTHESIS, OBJECTIVES, AND STUDY DESIGN

2.1 Hypothesis

I hypothesize that use of an antiplatelet agent will improve survival and reduce the need for ICU-level organ support in patients admitted to hospital for CAP. In patients with COVID-19, I hypothesize that exposure to an antiplatelet agent in combination with therapeutic-dose heparin will improve survival without ICU-level organ support compared with therapeutic-dose heparin alone.

2.2 Overall objective

My overall objective was to conduct foundational research that would evaluate the treatment effect and safety of antiplatelet agents, with or without therapeutic-dose anticoagulation, in different etiologies of CAP. This would provide foundational knowledge to inform the design of a future RCT of antiplatelet agents in CAP.

2.3 Study specific objectives

OBJECTIVE 1: To determine the efficacy and safety of antiplatelet agents in patients hospitalized with non-COVID-19 CAP.

Using the existing literature, we planned a systematic review and meta-analysis of published data to determine the overall treatment effect, event rates, and safety events (major bleeding) of patients hospitalized with non-COVID-19 CAP, exposed or not exposed to an antiplatelet agent. The purpose of this objective was to highlight on-going knowledge gaps and generate evidence that would support the rationale and design of future RCTs evaluating antiplatelets in CAP.

OBJECTIVE 2: To determine the efficacy and safety of antiplatelet agents in combination with therapeutic-dose heparin in non-critically ill patients hospitalized with COVID-19.

Therapeutic-dose heparin is an established treatment for non-critically ill patients hospitalized with COVID-19 CAP, but the effect of adding an antiplatelet agent remains uncertain. Using data from the mpRCT, we planned a secondary analysis using propensity weighted analyses to determine the effect and safety of combination antiplatelet agents with therapeutic-dose heparin on outcomes in non-critically ill patients with COVID-19, compared to therapeutic-dose heparin alone. Our group is currently conducting the ATTACC-CAP trial, a large platform trial evaluating therapeutic-dose heparin vs. usual care in CAP. The purpose of this objective was to inform the impact of adding an antiplatelet intervention to the platform, specifically in a multifactorial design (where patients would be randomized to therapeutic-dose heparin alone, antiplatelet agents alone, the combination of both, or usual care).

3.0 METHODS

This section provides a brief overview of the research methods used in both studies. Detailed research methods are highlighted in the included manuscripts, the study protocols and statistical analysis plans (Section 8.0).

3.1 Study 1: Efficacy and safety of antiplatelet agents in non-COVID-19 CAP

Study design and search strategy

We conducted a systematic review and meta-analysis to determine the overall efficacy and safety of antiplatelet agents in patients admitted to hospital with non-COVID-19 CAP. We used methodologic approaches outlined in the *Cochrane Handbook for Systematic Reviews* and reported them in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRIMSA) criteria.[49,50] The protocol was registered with Open Science Framework on January 30, 2024 (DOI https://doi.org/10.17605/OSF.IO/H2G7C) and published on a public preprint server (Section 8.1).[51] We searched Medline® (Ovid), Embase (Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to August 2023 to identify relevant citations of observational studies and RCTs. To identify planned, on-going, or recently completed RCTs, we searched clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP), and

abstracts from relevant conferences. We also searched reference lists of relevant narrative reviews, systematic reviews, and the included studies for additional citations.

Research question

In adult patients admitted to hospital for non-COVID-19 CAP, does exposure to an antiplatelet agent (ASA or P2Y12 inhibitors, at any dose or frequency of administration) during hospitalization reduce mortality from CAP, compared to those not receiving an antiplatelet agent?

Population

We included observational studies (retrospective and/or prospective) and RCTs of adult patients (age ≥ 18 years) hospitalized for non-COVID-19 CAP, for which host directed treatment with anticoagulation and/or antiplatelet agents are not standard of care. We excluded studies of hospital acquired pneumonia, ventilator associated pneumonia, quasi-randomized trials, and case-control studies.

Interventions and comparators

We included studies that compared patients who did and did not receive an antiplatelet agent. The intervention group included patients that received an antiplatelet agent (ASA or P2Y12 inhibitors clopidogrel, prasugrel, or ticagrelor) at any dose or frequency after study enrollment. Studies that included patients with antiplatelet exposure prior to study enrollment were included, regardless of the indication. The comparator group included patients receiving either placebo, usual care (open label), or a non-antiplatelet active comparator.

Outcomes

Our primary outcome was all-cause mortality reported at the longest duration of follow up. Secondary outcome measures included the need for ICU admission, hospital length of stay, use of invasive mechanical ventilation (IMV), use of any respiratory support (non-invasive ventilation (NIV) and/or high flow nasal oxygen (HFNO)), use of cardiovascular organ support, incidence of arterial thromboembolic events (MI and/or stroke), and incidence of venous thromboembolic events (VTE), including DVT and/or pulmonary embolism (PE). The primary safety outcome was incidence of major bleeding, which was author defined. For observational studies, we reported only adjusted effect estimates for the primary outcome to reduce possible confounding, and we reported

outcomes for observational studies and RCTs separately without pooling, as pre-specified in our protocol.[51]

Data analysis

Meta-analyses were conducted using random effect inverse variance models. In the meta-analysis of the primary outcome, study-level adjusted mortality estimates from observational studies were pooled and presented separately as adjusted hazard ratio (HR) and adjusted odds ratio (OR) with 95% confidence intervals (CI). Unadjusted study-level summary effect comparisons from RCTs were presented as risk ratios (RR) with 95% CI. Statistical heterogeneity was quantified using the I^2 statistic.[52] Analyses were conducted using the general meta and metafor package[53] in RStudio version 2023.09.1+494, R version, 4.3.2 (R project for Statistical computing). We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework to evaluate the strength of the evidence.[54]

3.2 Study 2: Efficacy and safety of antiplatelet agents in combination with therapeutic-dose heparin in COVID-19 CAP

Study design

We conducted a retrospective propensity-score adjusted secondary analysis of the mpRCT trial data. The mpRCT was a multicenter, international, adaptive RCT that included non-critically ill patients hospitalized for COVID-19 between April 2020 and January 2021 that were randomized across 2 trial platforms (ATTACC and ACTIV-4a). Patients were randomly assigned to receive therapeutic anticoagulation with either low molecular weight heparin or unfractionated heparin vs. usual care. The mpRCT federated the ATTACC and ACTIV-4a trial protocols and data, analyzing and reporting outcomes together in the mpRCT.[22,40] Since therapeutic-dose heparin was shown to improve survival with reduced ICU-level organ support, we focused our analysis on patients randomized to receive therapeutic-dose heparin.

Research question

In adult patients admitted to hospital for COVID-19 without critical illness, does the combination of therapeutic-dose heparin and an antiplatelet agent (ASA or P2Y12 inhibitor) improve survival without ICU-level organ support, compared to those receiving therapeutic-dose heparin alone?

Study population and treatment groups

We included all patients enrolled in the therapeutic-dose heparin arm of the mpRCT. Patients receiving organ support within an ICU or repurposed critical care area at trial screening were excluded. Treatment groups were defined as: 1) patients who received combination therapeutic-dose heparin and an antiplatelet agent (intervention group), and 2) patients who received therapeutic-dose heparin alone (control group). Therapeutic-dose heparin was administered according to local practice algorithms or guidelines for the treatment of VTE. Antiplatelet exposure was defined as receipt of at least one dose of ASA or a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) during hospitalization for COVID-19, regardless of the indication.

Outcomes

Our primary outcome was a composite ordinal outcome that reflected survival to hospital discharge without requiring organ support in an ICU. The 3-level ordinal scale included 1) survival to hospital discharge without ICU-level organ support (best outcome), 2) survival to hospital discharge with ICU-level organ support (intermediate outcome), and 3) in-hospital mortality (worst outcome), each evaluated at 21-days. Organ support was defined as receipt of HFNO, NIV, IMV, use of vasopressors and/or inotropes, or extracorporeal life support within an ICU. Our primary safety outcome was the incidence of major bleeding as defined by the International Society on Thrombosis and Haemostasis.[55]

Statistical analysis

We generated propensity scores to estimate a patient's probability of receiving an antiplatelet agent given their baseline characteristics.[56] Propensity scores were generated using a logistic regression model where exposure to an antiplatelet agent was regressed on 19 covariates (Section 8.3).[57,58] Clinicians and content experts confirmed the appropriateness of the included covariates based on their influence on the exposure (receipt of an antiplatelet agent) or the outcome.[59,60]

We assessed the ability of different propensity methods to achieve balance in measured covariates between treatment groups (Section 8.4). We calculated mean standardized differences for each covariate and considered an absolute standardized differences < 0.1 to have achieved adequate balance between treatment groups.[61] We also compared the distribution of propensity scores and

balance in covariates using histograms and cumulative density plots (Section 8.4).[58] We selected the stabilized inverse probability of treatment weighting (IPTW) analytic approach for our primary propensity model as it resulted in the best overall covariate balance between groups and used the most available patient data, compared to other propensity methods (Appendix 8.5).[62] The stabilized IPTW model was selected *a priori*, prior to estimating the treatment effect.

We used a proportional odds model to estimate the effect of exposure to an antiplatelet agent on the 3-level ordinal primary outcome. Effect comparisons were presented as odds ratio, where an OR > 1 for the primary outcome represented a greater odds of survival to hospital discharge without the need for ICU-level organ support.

A priori sensitivity analyses were planned to evaluate the treatment effect after controlling for possible residual confounding and by using different propensity analytic methods. First, we reanalyzed the treatment effect using stabilized IPTW after adding clinically important covariates that remained unbalanced after propensity weighting into the proportional odds model. Second, we re-estimated stabilized IPTW after accounting for possible non-linear relationships between unbalanced continuous variables and the probability of receiving an antiplatelet. Lastly, we re-estimated propensity scores using 2 other propensity analytic approaches: 1) propensity matching, and 2) propensity stratification. We then calculated the estimated treatment effect to compare the impact of different propensity methods on the overall treatment effect (Section 8.5).

4.0 STUDY SUMMARIES

This section provides a brief overview of the main findings from both studies. Detailed results and additional analyses are highlighted in the included manuscripts and supplementary materials (Sections 8.2, 8.4, and 8.5).

4.1 Study 1: Efficacy and safety of antiplatelet agents in non-COVID-19 CAP

Of the 7,696 citations identified, we included 13 observational studies (n=123,012) and 2 RCTs (n=225). Of the observational studies, five (38%) were prospective, eight were retrospective (62%), and most (85%) were published in peer-reviewed journals. The study level mean age was 70.1 (range 59.9 – 76.7) and the average proportion of females was 42%. At baseline, the proportion of

participants reported to have chronic respiratory diseases, cardiovascular diseases, and coronary artery disease was 28%, 26%, and 17%, respectively (Table 1).

Study quality and risk of bias

Most observational studies were adjudicated to be of high or intermediate quality (54% and 23%, respectively). Only six (46%) reported an adjusted effect estimate on mortality and were included in the primary analysis, to account for possible confounders. Both included RCTs were determined to be at high risk of bias.

Study exposures

Observational studies evaluated the effect of ASA (54%), clopidogrel (8%), or any antiplatelet agent (38%) in which most of the exposure was to ASA (Table 1). Dosing of ASA was predominantly low dose (≤ 100 mg/d). The comparator group was predominantly usual care. One RCT (n=198) randomized patients to ASA 300 mg/d vs. open-label usual care, and the second RCT (n=27) randomized patients to ASA 75 mg/d vs. placebo.

Table 1: Characteristics of individual trials, patient populations, and exposures

Study	Design	No. Patients APT/Control	Mean or median age	% female	% CAD	% CVD	% Severe CAP**	Type of APT (%)	Longest follow up (d)***
Bui 2022	Retrospective (conference proceeding)	117/336	72	52	22	NR	NR	Any APT (100) - Type NR	30
Cangemi 2014	Prospective	123/155	70	38	36	NR	NR	ASA (100)	NR
Chalmers 2008	Prospective	311/696	66	50	NR	20	NR	ASA (100)	30
Cilli 2018	Retrospective	111/262	68	42	NR	NR	100	Any APT (100) - ASA (74) - Alternative (26)	NR
Falcone 2015	Prospective	390/615	75	41	NR	31	NR	ASA (100)	30
Falcone 2019	Prospective	383/910	77	38	NR	26	100	ASA (100)	30
Gamst 2014	Retrospective (administrative data)	18,195/70,120	73	47	9	NR	7	ASA (100)	365
Gross 2013	Retrospective (administrative data)	2,908/20,974	NR	NR	NR	NR	NR	Clopidogrel (100)	NR
Lu 2023	Retrospective (administrative data)	182/580	NR	NR	NR	NR	100	ASA (100)	60
Nozzoli 2021	Prospective	455/811	76	49	17	NR	NR	Any APT (100) - Type NR	30
Peyrani 2016	Retrospective (Abstract)	639/2,698	NR	NR	NR	NR	NR	Any APT (100) - Type NR	30
Rognvaldsson 2022	Retrospective	128/687	67	48	17	NR	20	ASA (100)	365

Winning 2009	Retrospective	44/180	60	31	NR	NR	NR	Any APT (100) - ASA (86) - Clopidogrel (7) - Other (7)	28
Oz 2013	RCT	91/94	67	34	0	NR	NR	ASA (100)	30
Toner 2009	RCT	14/13	NR	NR	NR	NR	100	ASA (100)	90

APT = antiplatelet; C = control; CAD = coronary artery disease; CAP = community acquired pneumonia; CVD = cardiovascular disease; d = days; IQR = interquartile range; NR = not reported; SD = standard deviation
** Severe CAP was defined as a requirement for ICU admission for CAP
*** Longest follow-up for our primary outcome of mortality

Study outcomes

Adjusted all-cause mortality summary effect estimates from observational studies were meta-analyzed by hazard ratio (Figure 1) or adjusted odds ratio (Figure 2). Results from RCTs were pooled separately (Figure 3). Exposure to an antiplatelet agent was associated with a reduced risk of death in observational studies reporting hazard ratios (HR) compared to usual care (HR 0.65, 95% CI 0.46 – 0.91; I^2 85%; 4 studies; 91,430 patients). In studies reporting adjusted odds ratios (aOR), antiplatelet exposure was associated with a reduced odds of dying over the study period (OR 0.67, 95% CI 0.45 – 1.00; I^2 0%; 2 studies; 24,889 patients). The certainty of the evidence was low due to risk of bias in observational study designs, inconsistent effect estimates with heterogeneity in the pooled effect, and potential for publication bias (Table 2). In the 2 included RCTs (n=225), the relative risk of all-cause mortality in patients randomized to receive ASA compared to usual care or placebo was 0.66 (95% CI 0.20 – 2.25; I^2 54%). Forest plots are presented in Figures 1-3. The certainty of the evidence was low as both RCTs were at high risk of bias due to imprecision in the effect estimates (Table 2). Subgroup analyses were not associated with significant differences in treatment effect and did not reduce heterogeneity (Section 8.2).

Figure 1: Association of antiplatelet agents with mortality for observational studies reporting adjusted hazard ratios

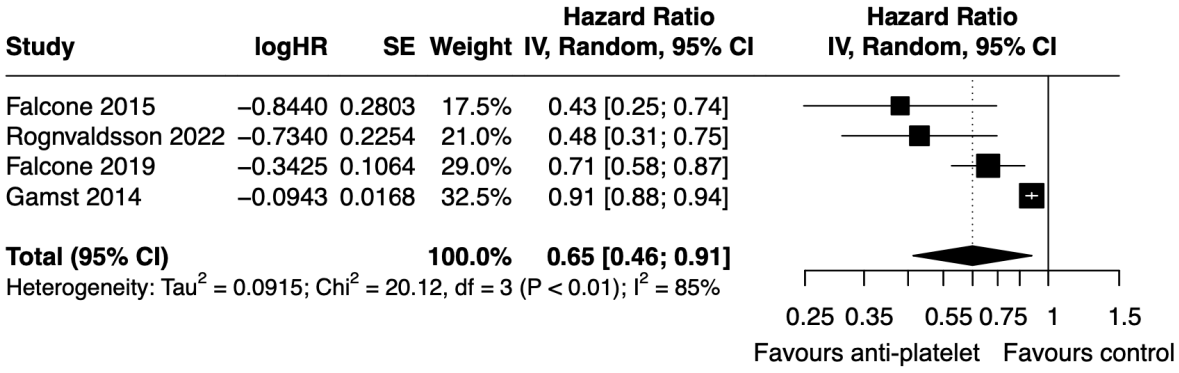


Figure 2: Association of antiplatelet agents with mortality for observational studies reporting adjusted odds ratios

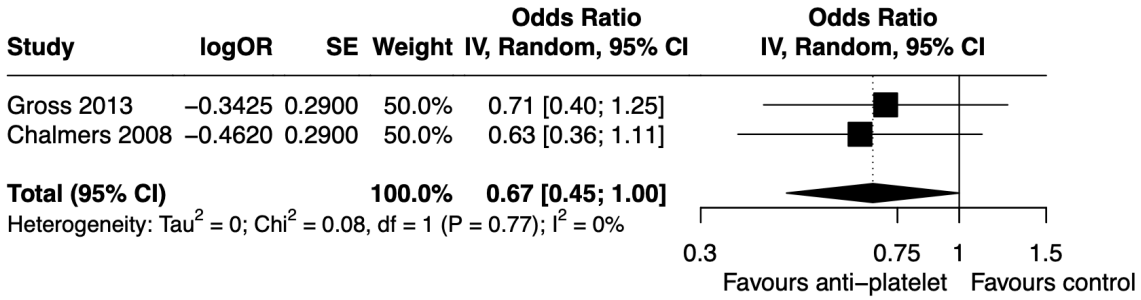
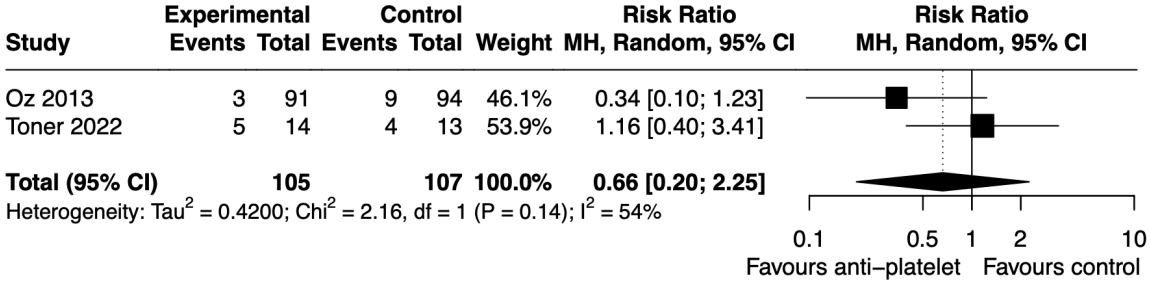


Figure 3: Association of ASA with mortality for RCTs reporting relative risk



ASA was not associated with an increased risk of bleeding, with no bleeding events recorded in either the treatment or control group as reported in a single RCT (n=185). This primary safety outcome was under reported in all included studies. Exposure to an antiplatelet agent was not associated with significant differences in any of the measured secondary outcomes (Table 2).

Table 2: Results from meta-analyses including summary effect measures, number of participants, and certainty of evidence

Outcome	Relative effect Adjusted HR (95% CI)	Relative effect Adjusted OR (95% CI)	Relative effect Unadjusted RR (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)
Observational Studies					
Adjusted mortality**	0.65 (0.46 – 0.91)			91,430 (4 studies)	Low
		0.67 (0.45 – 1.00)		24,889 (2 studies)	Low
ICU admission			0.91 (0.79 – 1.03)	25,854 (4 studies)	Very low
Use of IMV			0.96 (0.59 – 1.56)	25,177 (2 studies)	Very low
Use of any organ support			1.54 (0.78 – 3.03)	2,755 (3 studies)	Very low
Myocardial infarction			6.69 (0.16 – 271.55)	1,997 (3 studies)	Very low
Randomized Controlled Trials					
Mortality**			0.66 (0.20 – 2.25)	212 (2 RCTs)	Low
Myocardial infarction			0.10 (0.01 – 0.79)	185 (1 RCT)	Very low
Bleeding			No events	185 (1 RCT)	Very low

aOR = adjusted odds ratio; APT = antiplatelet; HR = hazard ratio; ICU = intensive care unit; IMV = invasive mechanical ventilation; RCT = randomized controlled trial; RR = risk ratio
**Primary outcome and primary analysis

4.2 Study 2: Efficacy and safety of antiplatelet agents in combination with therapeutic-dose heparin in COVID-19 CAP

We included 1,021 patients from the mpRCT who were randomized to receive therapeutic-dose heparin. The overall rate of concurrent antiplatelet agent exposure was 19% (n=194). The most used antiplatelet agent was ASA (n=186, 95.4%). At baseline, patients receiving therapeutic-dose heparin in combination with an antiplatelet agent were older, more likely female, and more likely to have baseline comorbidities such as cardiovascular disease, diabetes, and hypertension, compared to those receiving therapeutic-dose heparin alone (Table 3).

Table 3: Baseline characteristics of patients exposed and unexposed to an antiplatelet agent in patients randomized to receive therapeutic anticoagulation with heparin in the mpRCT before and after stabilized inverse probability of treatment weighting

	Unweighted cohort			**Weighted cohort post stabilized IPTW**			
Variable	TAC + APT (n=194)	TAC alone (n=827)	SD	TAC + APT (n=60)&	TAC alone (n=652)&	SD	%Δ SD
Age (years), mean (SD)	67.4 (11.6)	57.5 (14.0)	0.702*	62.0 (13.9)	59.7 (14.5)	0.163*	77
Female sex (%)	46.4	38.6	0.160*	37.8	39.1	-0.027	83
Race (%)							
White	52.1	54.7	-0.052	58.1	54.2	0.076	0
Asian	2.6	3.9	-0.069	1.2	3.3	-0.114*	0
Black	30.9	16.2	0.375*	18.8	18.7	0.001	100
Indigenous	1.5	12.2	-0.353*	1.6	1.0	-0.284*	20
Ethnicity (%)							
Hispanic or Latino	21.6	48.9	-0.548*	41.2	44.5	-0.067	88
BMI, mean (SD)	32.3 (7.8)	31.1 (7.7)	0.151*	31.8 (7.4)	31.2 (7.8)	0.081	46
Comorbidities (%)							
Immunosuppression	14.9	6.7	0.302*	7.9	8.2	-0.011	96
CVD	38.7	5.7	1.017*	15.3	13.3	0.061	94
Respiratory disease	27.3	15.7	0.302*	32.3	18.4	0.364*	0
Diabetes	51.0	24.9	0.571*	32.3	30.2	0.045	92
Hypertension	76.8	47.0	0.596*	52.9	53.1	-0.003	99
CKD	20.1	4.5	0.595*	9.0	8.9	0.004	99
Oxygen support (%)							
No oxygen	12.9	15.4	-0.069	23.6	15.3	0.233*	0
Low flow oxygen	74.2	76.7	-0.057	67.9	76.2	-0.195*	0
High flow oxygen	2.6	1.3	0.100*	1.1	1.4	-0.029	71
Co-treatments (%)							
Corticosteroids	10.3	5.0	0.226*	9.1	5.2	0.165*	27
Remdesivir	0.5	0.2	0.051	0.2	0.2	-0.006	88
Lab values mean (SD)							
Creatinine (mg/dL)	1.4 (1.9)	1.0 (0.8)	0.341*	1.2 (1.3)	1.1 (1.0)	0.027	92
Platelets (x 10^9)	216 (80)	243 (103)	-0.272*	224 (81)	236 (102)	-0.124*	54
D-dimer (ULN)#	4.1 (8.5)	2.6 (4.3)	0.276*	2.7 (5.1)	2.7 (4.2)	-0.005	98
Country (%)							
Brazil	8.8	26.2	-0.416*	22.3	23.0	-0.017	96
Canada	11.9	9.2	0.090	7.6	9.4	-0.061	32
United States	77.3	47.3	0.602*	67.0	53.4	0.273*	55

*Absolute SD > 0.1; & effective sample size after weighting; # d-dimer was measured as the a ratio above the ULN according to local laboratory criteria; %Δ SD = absolute percentage reduction in standardized difference; APT = antiplatelet; BMI = body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease; IPTW = inverse probability of treatment weighting; SD = standardized difference; TAC = therapeutic-dose anticoagulation; Var ratio = variance ratio

Performance of the propensity analysis

Absolute standardized differences exceeded 0.1 in 76% of variables at baseline. Following propensity score estimates and conversion to stabilized IPTW, the mean stabilized IPTW was 0.816 (SD 1.220, range 0.190 – 12.220) in the intervention group and 1.009 (SD 0.523, range 0.810 – 7.580) in the control group demonstrating no concrete evidence of non-positivity or mis-specification of the propensity scores. After weighting, the median absolute standardized differences were < 0.1 indicating adequate balance in covariates between treatment groups (Section 8.4).

Estimation of treatment effects

Exposure to an antiplatelet agent was not associated with an improvement in survival without ICU-level organ support in patients receiving therapeutic-dose heparin (OR 1.07, 95% CI 0.71 – 1.64). Of the patients in the intervention group 76.3% survived to hospital discharge without ICU-level organ support compared to 80.5% in the control group. Exposure to an antiplatelet was not associated with any significant differences in secondary outcomes, including major bleeding events. Patients receiving combination treatment had a numeric increase in the number of major bleeding events compared with the control group (4.1 vs. 1.0%, OR 1.69, 95% CI 0.43 – 5.19). All sensitivity analyses yielded similar treatment effects, with no significant differences observed in the primary outcome (Section 8.5).

5.0 DISCUSSION

5.1 Principal findings

In our systematic review and meta-analysis, we summarized the available literature reporting the association of antiplatelet agents on mortality in patients with non-COVID-19 CAP. We identified only 2 RCTs (n=225) and 13 observational studies. The exposure to an antiplatelet agent was possibly associated with an improvement in mortality. In observational studies, antiplatelet agents were associated with a 35% lower adjusted hazard of death. Among two small included RCTs, randomization to ASA was associated with a similar but non-significant reduction in the relative risk of mortality compared with usual care or placebo. The certainty of the included evidence was low, and inferences were difficult to ascertain due to small sample sizes, low event rates, and considerable risk of bias. An increased risk of bleeding was not identified; however, this outcome was under reported. Experience with ASA in hospitalized COVID-19 patients would suggest an expected absolute increase in major bleeding events of 0.6 – 0.8%.[43,45]

In our secondary analysis of the mpRCT, we used a propensity weighted analysis to evaluate the effect of antiplatelet agents in combination with therapeutic-dose heparin in non-critically ill patients hospitalized with COVID-19. The exposure to an antiplatelet agent did not significantly improve survival to hospital discharge without ICU-level organ support in patients receiving therapeutic-dose heparin. Fewer patients in the combination treatment group survived to hospital

discharge without ICU-level organ support, compared to therapeutic-dose heparin alone (76.3 vs. 80.5%). While major bleeding events were numerically higher in the treatment group, total events were low and predominantly driven by the need for blood transfusion.

5.2 Implications in the context of current evidence

This thesis has generated key evidence to inform further evaluation of antiplatelet agents through future interventional trials. Treatment for CAP has not substantially changed in several decades,[63,64] but therapeutic-dose heparin and antiplatelet agents are promising therapies that may attenuate the host response to infection and improve end organ dysfunction and survival in CAP. Herein, we summarize the literature evaluating therapeutic dose-heparin alone, antiplatelet agents alone, and their use in combination, in both COVID-19 and non-COVID-19 pneumonia.

5.2.1 Therapeutic-dose heparin in CAP

COVID-19 CAP

A significant body of evidence supports improved outcomes with therapeutic-dose heparin in non-critically ill patients with COVID-19. The mpRCT found that, compared to usual care thromboprophylaxis, therapeutic-dose heparin reduced the composite ordinal endpoint of progression to ICU-level organ support and death in hospitalized, noncritically ill patients (n=2,219) with COVID-19.[22] The probability that therapeutic-dose heparin increased organ support-free days as compared with usual care was 98.6% (median aOR 1.27, 95% CrI 1.03 – 1.58). Patients randomized to therapeutic-dose heparin survived to hospital discharge without ICU-level organ support in 80%, as compared to 76% of patients randomized to usual care (absolute risk reduction 4%). Major bleeding events were low in both the treatment and control groups (1.9 vs. 0.9%), and 85% of the major bleeding events were driven by the need for red blood cell transfusion, as opposed to critical site or fatal bleeding.[22] In a simultaneous publication, therapeutic-dose heparin was not beneficial in patients who started treatment after the onset of critical illness.[40]

These findings have been replicated in other RCTs. The RAPID trial observed similar reductions in mortality and the need for respiratory organ support in non-critically ill patients with COVID-19 treated with therapeutic-dose heparin compared with usual care thromboprophylaxis.[41] A meta-analysis of the mpRCT, RAPID, and other therapeutic-dose heparin trials in COVID-19 demonstrated consistent reductions in mortality and/or invasive mechanical ventilation (OR 0.77,

95% CI 0.60 – 0.98).[65] Therapeutic-dose heparin is now a widely accepted host directed treatment for hospitalized COVID-19 patients, prior to the onset of critical illness, as supported by multiple international clinical practice guidelines.[66-69] Whether therapeutic-dose heparin could yield similar benefits in patients with other etiologies of CAP remains uncertain.

Non-COVID-19 CAP

The clinical utility of therapeutic-dose heparin in non-COVID-19 CAP has never been studied in an RCT. Nonetheless, a significant body of evidence including laboratory data,[70] animal models,[71] observational studies,[72] and RCTs in humans support the potential for therapeutic-dose heparin to reduce mortality in other severe infectious syndromes like sepsis and septic shock. In a meta-analysis of six trials that evaluated therapeutic-dose heparin vs. placebo or usual care in patients with sepsis and septic shock (n=2,477), therapeutic-dose heparin was associated with a 12% relative reduction in the risk of death (RR 0.88, 95% CI 0.77 – 1.00).[73] Similarly, a second meta-analysis of 17 randomized trials (n=1,167) enrolling patients with sepsis demonstrated decreased 28-day mortality with therapeutic-dose heparin (OR 0.59, 95% CI 0.45 – 0.77).[74] Importantly, heparin was not associated with increased risk of major bleeding. [73,74]

Leveraging the supportive literature and knowledge generated in COVID-19, evaluation of therapeutic-dose heparin in other etiologies of CAP is a high priority. The ATTACC-CAP clinical trial is a large, international, Bayesian adaptive trial that is currently enrolling non-critically ill patients hospitalized with CAP from any etiology (NCT05848713). Patients with CAP requiring oxygen are considered for inclusion, and those with suspected or proven COVID-19, or those at high risk of bleeding are excluded. Patients are randomized to receive therapeutic-dose heparin vs. usual care thromboprophylaxis for up to 14 days, or until hospital discharge, whichever comes first. The primary objective of the trial is to evaluate the effect of therapeutic-dose heparin on preventing ICU admission and improving survival, as measured by an ordinal primary outcome scale. The trial includes a network of 60+ sites across 3 countries and is anticipated to enrol up to 3,500 patients over the next 3-4 years. The trial is actively enrolling patients (Canada, USA, Brazil), with plans to add additional interventions to the platform and expand to additional sites, countries, and other trial networks.

5.2.2 Antiplatelet agents in CAP

COVID-19 CAP

Four large RCTs evaluated antiplatelet agents in hospitalized COVID-19 patients demonstrating mixed results.[43,45,46,48,75] In the REMAP-CAP Bayesian adaptive platform trial (n=1,546), critically ill patients randomized within the antiplatelet domain had a 95% probability of improved 6-month survival (HR 0.85, 95% CrI 0.71 – 1.03).[46] In the RECOVERY trial (n=14,892), ASA was not associated with a reduction in mortality at 28 days (RR 0.96, 95% CI 0.89 – 1.04) or a difference in the proportion of patients who required ventilation or died (RR 0.96, 95% CI 0.90 – 1.03), but there was a significant reduction in thrombotic events (4.6 vs. 5.3%, absolute difference -0.6%, standard error 0.4%).[45] The COVID-PACT (n=292) and ACTIV-4a (n=1,549) trials did not demonstrate significant benefit with ASA or P2Y12 inhibitors.[43,75] The risk of major bleeding was small but increased among patients randomized to receive antiplatelet agents. In the context of inconsistent results, antiplatelet agents are not currently recommended in COVID-19.[69]

Non-COVID-19 CAP

Very limited data suggests that antiplatelet agents could improve outcomes from infectious diseases. A meta-analysis of RCTs evaluating the effect of ASA in acute infections demonstrated an association with reduced mortality (RR 0.44, 95% CI 0.24 – 0.81; 4 RCTs; 538 patients).[76] This study only included 1 RCT of patients with CAP.[33] Our systematic review adds to this body of evidence suggesting that exposure to an antiplatelet agent during hospitalization for CAP could be associated with a reduced risk of mortality. However, there remain several important unanswered questions, both in COVID-19 and non-COVID-19 CAP. The effect of specific types of antiplatelets, dose, duration of exposure, impact of disease severity, and effect on longer term outcomes remain uncertainties that necessitate further investigation.

5.2.3 Combination treatment with therapeutic-dose heparin and antiplatelet agents in CAP

COVID-19

The Bayesian adaptive ACTIV-4a trial (n=562) randomized patients to receive therapeutic-dose heparin plus a P2Y12 inhibitor (63% ticagrelor, 37% clopidogrel) vs. therapeutic-dose heparin alone. Combination treatment did not improve the number of organ support-free days (aOR 0.83, 95% CrI 0.55 – 1.25, propability of inferiority 81%). Major bleeding occurred in 6 vs. 2 patients in the treatment and control groups, respectively.[48] Our secondary analysis of the mpRCT adds to the

overall evidence that combination treatment with an antiplatelet yields no additional benefit relative to therapeutic-dose heparin alone. Our analysis included predominantly patients receiving ASA, as opposed to P2Y12 inhibitors evaluated in the ACTIV-4a trial, suggesting no significant influence on the type of antiplatelet used. Given therapeutic-dose heparin is not an accepted treatment for non-COVID-19 CAP, data supporting the use of combination anticoagulation and antiplatelet agents in CAP is limited.

5.3 Informing future research

The COVID-19 pandemic rapidly generated evidence supporting host directed therapies to reduce organ dysfunction and improve survival in hospitalized patients with COVID-19.[22,37,38] Given the strong body of evidence supporting therapeutic-dose heparin,[22] this treatment is now being evaluated in other etiologies of CAP. The first active domain in the ATTACC-CAP trial is evaluating therapeutic-dose heparin vs. usual care thromboprophylaxis in non-COVID-19 CAP, building off the findings in COVID-19. This thesis provides important foundational evidence that will help inform the addition of future interventions within the ATTACC-CAP platform.

In study 1, our meta-analysis suggested a possible beneficial treatment effect with antiplatelets in non-COVID-19. Given the low quality of the available literature, we concluded that high quality RCTs are needed to better evaluate the overall treatment effect. The ATTACC-CAP platform trial provides a unique opportunity to add an antiplatelet domain, where non-critically ill patients hospitalized with non-COVID-19 CAP could be randomized to receive an antiplatelet agent vs. usual care and evaluate the effect of antiplatelets on prevention of ICU-level organ support, survival, and bleeding risk. Most platform trials with more than one treatment domain use a multifactorial design, where a single patient can be randomized to multiple interventions within the same trial. Benefits of this design includes testing of multiple interventions simultaneously and avoiding the requirement of a second comparator group for each two-way comparison. Additionally, since the trial is adaptive, studying more than one intervention at once allows for continuation of the trial once conclusions are reached at interim analyses for other treatment domains.[77,78] Given the findings in Study 1 and supporting literature, we considered adding an antiplatelet agent intervention within ATTACC-CAP with a multifactorial design, where patients could be randomized to receive therapeutic-dose anticoagulation alone, an antiplatelet agent alone, both in combination, or usual care.

Study 2 provided insight into the treatment effect and safety of antiplatelet agents in combination with therapeutic-dose heparin in patients with CAP. Since therapeutic-dose heparin is now a standard of care treatment in COVID-19, we utilized this population to evaluate the treatment effect and safety of combination therapy. The results of our secondary analysis suggested that the addition of an antiplatelet to therapeutic-dose heparin likely does not improve outcomes. While bleeding events were generally low, major bleeding was numerically increased in those receiving combination therapy, as might be expected. These findings are consistent with other published literature in COVID-19, where combination P2Y12 inhibitors with therapeutic-dose anticoagulation had a high probability of inferior outcomes, with increased bleeding.[48]

Taken together, the findings of this thesis suggest that antiplatelet agents could be beneficial in CAP. However, given an unlikely benefit and concerns over bleeding in patients exposed to a combination antiplatelets and therapeutic-dose heparin, use of a factorial design with simultaneous evaluation of both treatments within ATTACC-CAP might be avoided.

Several alternatives can be considered to generate knowledge for both treatments. Patients could be randomized to either therapeutic-dose heparin alone, an antiplatelet agent alone, or usual care within the same domain. This approach would avoid a combination treatment group, but would also increase the timelines of the trial, necessitating more patients to answer both questions. Alternatively, survivors of acute hospitalization for CAP could be randomized to receive an antiplatelet agent vs. usual care upon discharge from hospital. Since therapeutic-dose heparin is ceased upon hospital discharge (or after a maximum of 14 days of treatment in hospital) in the ATTACC-CAP trial, the addition of an antiplatelet upon discharge would provide continued anti-inflammatory and antithrombotic treatment in the outpatient setting, when risks for cardiovascular events, re-hospitalization, re-infection, and death remain high.[25] Such an intervention could be added to the adaptive platform trial CLEAR-HORIZONS, which is a modular adaptive platform trial that is co-designed with ATTACC-CAP, to provide a post-discharge platform for CAP survivors and evaluate interventions to reduce post-hospitalization complications. Lastly, therapeutic-dose heparin and antiplatelet agents could be evaluated sequentially, once the effect of therapeutic-dose heparin is known.

5.4 Strengths and limitations

5.4.1 Strengths

The key strength of this thesis was the use of comprehensive multi-modal research methods to summarize evidence and generate knowledge that will help inform a future interventional clinical trial of antiplatelet agents in CAP. Our systematic review addressed an important clinical question by summarizing the current evidence for antiplatelet agents in non-COVID-19 CAP and remaining knowledge gaps. This project has been peer reviewed and published in an open access journal, and presented at national conferences for knowledge dissemination. Our secondary analysis of the mpRCT built upon the findings of our meta-analysis. Both therapeutic-dose heparin and antiplatelet agents could play a role in the future treatment of CAP. Understanding their effect in combination, and balancing the risk/benefit profile, is critically important to plan future clinical trials to generate evidence needed to inform practice.

Our systematic review utilized a comprehensive search strategy which included electronic databases, conference abstracts, trial registries, and forward searches following recognized methodologic guidelines for the conduct and reporting of systematic reviews. The conduct of the review was guided by a strong and diverse team of experts in the content and methods covered in the analysis. Study outcomes were patient-centered, were followed out to longest durations of follow-up, and included the evaluation of safety related to the intervention. We included and summarized the literature of a very broad population of CAP, including studies of respiratory failure, bacteremia, and sepsis, if treatment effects were reported in the exposed and unexposed treatment groups in the subset of patients with CAP. The broad inclusion of various CAP populations increases the generalizability of the findings to a large population of CAP.

Our secondary analysis of the mpRCT used a robust prospectively collected clinical trial dataset which reliably captured patient factors that could influence the exposure to an antiplatelet agent, and thus we were able to control for possible confounding through propensity weighting. We used and compared the results from several comprehensive analytic approaches including inverse probability weighting and matching, along with several sensitivity analyses, increasing the confidence in the findings.

5.4.2 Limitations

In our systematic review, we included observational studies due to the shortage of RCTs evaluating antiplatelet use in CAP. Inclusion of observational studies in meta-analyses of treatment effects confers risk due to imbalances between treatment groups and potential for confounding. Patients exposed to an antiplatelet may have had greater risk of poor outcomes due to a higher prevalence of comorbidities, advanced age, and disease severity factors. While we prioritized adjusted effect estimates in our primary analysis, statistical models controlled for different covariates between studies, raising concern for residual confounding. We also couldn't derive a single effect estimate as each included study reported different effect measures (HR and OR), limiting the confidence in our results. Publication bias could not be assessed due to the small number of included studies. Due to these limitations, we evaluated the quality of the evidence using established methodological guidelines with GRADE criteria and judged the quality of the evidence to be low. Additionally, due to limitations in the literature, our meta-analysis could not analyze the effect of different types of antiplatelet agents (ASA vs. P2Y12 inhibitors), the dose, the duration of use, the indication for use, and meaningful subgroup analyses (e.g.: in patients with specific CAP etiologies or varying disease severities). Evaluation of effect estimates at longer durations of follow up were also limited. Taken together, these limitations limit our confidence in the findings, and further high quality RCTs are required to address these remaining knowledge gaps.

While our secondary analysis of the mpRCT used comprehensive baseline and demographic data, the study populations were substantially different at baseline, requiring large weights to yield between group balance in covariates in our pseudo-population. To mitigate this, we used stabilized IPTW, standardized to the overall mean of the propensity score. While this yielded adequate balance in most covariates in our pseudo-population, not all covariates were balanced, leaving the potential for residual confounding in the estimated effect measure. After weighting, the remaining effective sample size within the intervention group was small (n=60), reducing the power in the estimate of the treatment effects. Additionally, our analysis was conducted in a clinical trial population with COVID-19 which was selected to meet specific inclusion and exclusion criteria within the trial, limiting the application of the findings to all comers with CAP. Lastly, we were unable to estimate the treatment effects at longer durations of follow up (180 days).

6.0 CONCLUSIONS

CAP is associated with a very high morbidity and mortality globally, with no effective treatments outside of supportive care and antimicrobials. Very few advances in the management of CAP have been made over the last few decades, and mortality rates remain unacceptably high. Given the pathophysiologic mechanisms presented, host-directed therapies targeted to attenuate maladaptive inflammatory and thrombotic responses to infection are promising.

Antiplatelet agents are widely available, inexpensive, and familiar, with well-established safety profiles. They have been shown to be efficacious in treatment of coronary artery disease and many other clinical syndromes which involve the pro-thrombotic and pro-inflammatory pathways, although its role in the treatment of serious infections remains uncertain.

In this thesis, we demonstrated that antiplatelet agents may be associated with reduced mortality in hospitalized patients with non-COVID-19 CAP, but the certainty of the evidence was low. Bleeding events were low, but under-reported, and can be anticipated to be slightly higher than patients without antiplatelet exposure. Further high quality RCTs are needed to evaluate the risk / benefit effects more comprehensively. We also demonstrated that combination treatment with antiplatelets and therapeutic-dose heparin in COVID-19 is not beneficial, with numerically higher bleeding events.

Taken together, further evaluation of both therapeutic-dose heparin and antiplatelet agents in CAP is a high priority. The ATTACC-CAP platform trial provides a unique clinical trial infrastructure to study both, however a multifactorial design exposing patients to combination anticoagulation and antiplatelet might be avoided. Alternative clinical trial designs should be considered for future evaluations of these promising therapies.

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8.0 SUPPLEMENTARY MATERIALS

This section includes the written and/or published protocols and manuscripts for the thesis studies and provides a detailed explanation of the research methods, results, and implications.

8.1 Study 1 protocol

Lother SA, Tennenhouse LG, Rabbani R, Abou-Setta AM, Askin N, Turgeon AF, Murthy S, Houston BL, Houston DS, Mendelson AA, Rush B, Rimmer E, Marshall JC, Shaw SY, Lawler PR, Keynan Y, Zarychanski R. The effect of anti-platelet agents on end organ dysfunction and mortality in community acquired pneumonia: A protocol for a systematic review and meta-analysis. *med*R*xiv*. Apr 2024: 2024.04.16.24305938

TITLE PAGE

Title: The effect of anti-platelet agents on end organ dysfunction and mortality in community acquired pneumonia: A protocol for a systematic review and meta-analysis

Sylvain A. Lother[1,2], Lana Tennenhouse[3], Rasheda Rabbani[4], Ahmed M. Abou-Setta[4], Nicole Askin[5], Alexis F. Turgeon[6,7], Srinivas Murthy[8], Brett L. Houston[9], Donald S. Houston[9], Asher A. Mendelson[2], Barret Rush[2], Emily Rimmer[9], John C. Marshall[10], Souradet Y. Shaw[11], Patrick R. Lawler[12,13], Yoav Keynan[1,14], Ryan Zarychanski[2,9]

Affiliations:

1 Section of Infectious Diseases, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
2 Section of Critical Care, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
3 Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
4 George & Fay Yee Centre for Healthcare Innovation, University of Manitoba, Winnipeg, Manitoba, Canada
5 Neil John Maclean Health Sciences Library, University of Manitoba, Winnipeg, Manitoba, Canada
6 Department of Anesthesiology and Critical Care, Université Laval, Quebec City, Quebec, Canada
7 Population Health and Optimal Health Practices Research Unit, Departments of Traumatology, Emergency Medicine, and Critical Care Medicine, Université Laval Research Center, CHU de Quebec-Université Laval, Quebec City, Quebec, Canada
8 Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada
9 Department of Medical Oncology and Hematology, CancerCare Manitoba, Winnipeg, Manitoba, Canada
10 Department of Surgery, University of Toronto, Toronto, Ontario, Canada
11 Department of Community Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
12 University of Toronto, Peter Munk Cardiac Centre at University Health Network, Toronto, Ontario, Canada
13 McGill University Health Centre, Montreal, Quebec, Canada
14 Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada

Protocol: Version 1.4
Date: February 27, 2024

Corresponding author: Dr. Sylvain A. Lother
University of Manitoba, Health Sciences Center
GC 436, level 4, 820 Sherbrook St, Winnipeg, MB, R3A1R9
+1-(204)-787-2767, Sylvain.Lother@umanitoba.ca

ABSTRACT

Background: Community acquired pneumonia (CAP) is a common cause of morbidity and mortality globally. Poor outcomes are driven by maladaptive inflammatory and thrombotic host responses. Effective therapies that modulate host responses are lacking. Anti-platelet medications modulate thrombotic and inflammatory pathways and improve long term outcomes in COVID-19 pneumonia, however, the role of anti-platelets in other etiologies of CAP remains uncertain.

Methods: We will conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) and observational studies including adult patients hospitalized for non-COVID-19 community acquired pneumonia (CAP) investigating the effect of anti-platelets (ASA or P2Y12 inhibitors) vs. control on all-cause mortality. We will search electronic databases including MEDLINE® (Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), clinical trial registries (clinicaltrials.gov, International Clinical Trials Registry Platform) and conference abstracts from inception to August 2023. Two blinded reviewers will extract data in parallel from included studies after title and abstract screening and application of eligibility criteria. We will use the Cochrane Risk of Bias tool and Newcastle Ottawa Scale to assess risk of bias and study quality from included studies. The primary meta-analysis will be conducted separately for RCTs and observational studies using Random effect inverse variance model. For observational studies, adjusted mortality estimates will be presented as hazard ratios (HR) or adjusted odds ratios (OR) whenever possible. Heterogeneity will be expressed using the I^2 statistic. The

evidence will be evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework.

Discussion: The overall treatment effect and safety of anti-platelets in non-COVID-19 CAP will be summarized. The findings may be used to inform the relevance and potential study design of a future RCT evaluating anti-platelets in CAP. If anti-platelets are shown to be safe and effective, this research is expected to contribute to a new standard of treatment for CAP, and a paradigm shift towards targeting host responses in serious infections.

Systematic Review Registration: This protocol is reported in accordance with the guidelines produced by PRISMA-P. The protocol was registered with Open Science Framework on January 30, 2024 (DOI https://doi.org/10.17605/OSF.IO/H2G7C)

KEY WORDS

Community acquired pneumonia, anti-platelets, aspirin, ASA, clopidogrel, mortality

BACKGROUND

Community acquired pneumonia (CAP) is a life-threatening lung infection and leading cause of hospitalization and mortality globally, accounting for 2.6 million annual deaths.[1,2,3] Among hospitalized patients with CAP, 30-day overall mortality is 23%[4] and 6-21% of patients require Intensive Care Unit (ICU) admission.[5,6]

Poor clinical outcomes in CAP are driven by maladaptive inflammatory and thrombotic host responses to infection. Respiratory pathogens activate the innate immune system, driving local and systemic inflammation and hypercoagulability through platelet activation, endothelial dysfunction, and immunothrombotic mechanisms, that persist for days to months after infection.[7,8] Excessive inflammation and coagulation contribute to organ dysfunction due to micro and macro-vascular thrombosis.[9,10]

Vascular thrombosis risk is elevated in CAP and occurs in approximately 11% of patients at 30-days.[11-13] An increased risk of venous thromboembolism (VTE) was seen in COVID-19,[14,15] and the incidence of symptomatic VTE in COVID-19 and CAP is comparable (2.0% vs. 3.6%, respectively), and higher in mechanically ventilated patients.[16] Influenza may be associated with an even greater risk of arterial thrombosis compared with COVID-19 (7.5% vs. 4.4%, respectively).[11] Cardiovascular events, often driven by vascular thrombosis, complicate CAP in up to a third of hospitalizations and these events are associated with a greater than 3-fold increase in mortality.[4,13,17]

Effective therapies that modulate the host response are lacking. Anti-platelet agents including acetylsalicylic acid (ASA) and P2Y12 inhibitors such as ticagrelor, clopidogrel, and prasugrel are familiar and widely accessible medications that have pleotropic effects with anti-thrombotic and anti-inflammatory activity. These mechanisms hold promise in blunting host immunothrombotic responses to infection.

In patients hospitalized with COVID-19 pneumonia, ASA demonstrated mixed effects in clinical trials, some showing benefit and others showing no significant effect.[18-20] Further analyses suggests that ASA may benefit individuals at longer follow up duration (180-day).[21] In non-COVID-19 pneumonia, a small randomized control trial (RCT) showed ASA reduced myocardial infarction (MI) and cardiovascular death in hospitalized patients.[22] Several other retrospective and prospective cohort studies have suggested a potential benefit with anti-platelet agents, however due to the heterogeneity of CAP, mixed results, and differing populations, the overall effect of anti-platelet agents in hospitalized patients with CAP remains uncertain.[23-25]

The purpose of this systematic review and meta-analysis is to evaluate the effect of anti-platelet agents on mortality, end organ failures, cardiovascular events, and bleeding for patients hospitalized with non-COVID-19 CAP. This protocol is reported in accordance with the guidelines produced by the Preferred Reporting items for Systematic Reviews and Meta-analysis for developing review protocols (PRIMSA-P).[26]

Methods/Design

We will conduct a systematic review using methodological approaches outlined in the *Cochrane Handbook for Systematic Reviewers* and report the findings in accordance with the Preferred Reporting items for Systematic Reviews and Meta-analysis (PRISMA) criteria for RCTs, and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria for observational studies.[27-29] The review question and methods have been constructed with experts in infectious diseases (AK, SL, SM, YK), critical care (AK, AM, AT, BR, JM, PL, SL, SM, RZ), hematology and thrombosis (BH, DH, EM, RZ), cardiology (PL), community health (SS), and knowledge synthesis methodology (AMAS, AT, JM, NA, RR, PL, SM, SS, RZ, YK). The roles of each team member are summarized in **Appendix 1**.

Eligibility criteria

The PICO statement and eligibility criteria for studies to be included or excluded from the systematic review and meta-analysis are provided in **Table 1** and **Table 2**.

Table 1: PICO statement

P - patients	Adults aged ≥ 18 years admitted to hospital for non-COVID-19 CAP
I - interventions	Patients exposed to an anti-platelet agent (ASA or P2Y12 inhibitors)
C - comparators	Patients not exposed to an anti-platelet agent
O - outcomes	Mortality, end-organ failures, and thromboembolic complications

CAP, community acquired pneumonia

Table 2: Eligibility criteria for studies to be included or excluded from the systematic review and meta-analysis

	Inclusion criteria	Exclusion criteria
Study design	RCTs (including placebo controlled and open label) and observational studies (including retrospective, prospective, and bi-directional cohort studies)	Animal studies, case-control studies, cross-over studies, cluster randomized trials
Participants	Comparative studies of adult patients admitted to a hospital for non-COVID-19 CAP (author defined), and studies of patients with bacteremia, sepsis, acute lung injury, and/or acute respiratory distress syndrome that report comparative effectiveness data for at least one clinical outcome in the CAP subgroup (derived CAP population with exposure to an APT vs. not)	Studies who enrol ≥ 20% of patients with URTI without evidence of LRTI, ≥ 20% with hospital acquired pneumonia (author defined), or ≥ 20% of CAP caused by COVID-19
Interventions	Studies where participants received ASA or a P2Y12 inhibitor, at any dose or frequency of administration, and regardless of whether the APT was received prior to hospitalization	Studies where ≥ 20% of patients are receiving DAPT, ≥ 20% of patients are receiving an APT in conjunction with therapeutic-dose anticoagulation
Comparator	Patients not receiving an APT (placebo, standard of care, no intervention, or another non-APT intervention)	Active comparator studies (one APT compared to another APT)
Outcomes	Primary outcome: • All-cause mortality (longest follow up) Secondary outcome: • ICU admission • Hospital LOS (days) • Use of IMV • Use of cardiovascular organ support (vasopressors and/or inotropes and/or ECLS) • Use of any organ support (composite including use of HFNO and/or NIPPV and/or IMV and/or vasopressors and/or inotropes and/or ECLS • Arterial thromboembolic event (myocardial infarction and/or stroke) • Venous thromboembolic event (deep venous thrombosis and/or pulmonary embolism) • Major bleeding	None of the listed outcomes are available from the study report(s) or through communication with the study authors
Setting	All hospital settings where patients with CAP are cared for	Patients cared for in personal care homes, long term care, or other non-hospital settings

APT = anti-platelet; ASA = acetyl salicylic acid; CAP = community acquired pneumonia; DAPT = dual anti-platelet; ECLS = extracorporeal life support; HFNO = high flow nasal oxygen; IMV = invasive mechanical ventilation; LOS = length of stay; LRTI = lower respiratory tract infection; NIPPV = non-invasive positive pressure ventilation; RCT = randomized controlled trial; URTI = upper respiratory tract infection

Study design and setting

We will include parallel design RCTs (including placebo controlled and open label trials) and observational studies (including retrospective, prospective, and bi-directional study designs), presenting comparative data on the exposure and the non-exposure to the intervention in a population of patients hospitalized for non-COVID-19 CAP. The required study setting will be in hospital. Studies that include patients cared for in personal care homes, long term care, or other non-hospital settings will be excluded.

Participants

We will include comparative studies of hospitalized adult patients (>80% of the study population is ≥ 18 years old) admitted to hospital for non-COVID-19 CAP. The diagnosis of CAP will be author defined and may include clinical or administrative definitions. Studies of patients with bacteremia, sepsis, acute lung injury, and/or acute respiratory distress syndrome that report on comparative effectiveness data for at least one clinical outcome in the CAP subgroup (derived CAP population with exposure to an anti-platelet vs. not) will also be included.

Interventions and comparisons

Studies where patients received an anti-platelet agent (ASA or P2Y12 inhibitors, at any dose or frequency of administration) after study enrollment, regardless of whether the anti-platelet agent was received prior to hospitalization will be included. These patients will comprise the intervention group. Patients not receiving anti-platelet agents (may be receiving placebo,

standard of care, no intervention, or another non-antiplatelet (non-ASA or non-P2Y12 inhibitor) intervention) will comprise the comparator group.

Outcomes

Each outcome for RCTs and observational studies will be reported separately (not pooled) due to the inherent differences in study designs, and outcomes will be reported at longest available follow-up. The primary outcome will be all-cause mortality. For observational studies, the adjusted effect estimate on mortality will be reported as the primary analysis whenever possible, to control for possible confounding. Secondary outcome measures will include arterial thromboembolic events (myocardial infarction and/or stroke), venous thromboembolic events (deep venous thrombosis and/or pulmonary embolism), ICU admission, hospital length of stay, use of invasive mechanical ventilation (IMV), use of cardiovascular organ support (vasopressors and/or inotropes and/or extracorporeal life support), use of any organ support (composite outcome including use of non-invasive positive pressure ventilation (NIPPV) and/or IMV and/or vasopressors and/or inotropes and/or extracorporeal life support). NIV includes the use of high flow nasal oxygen (NFNO) defined as flow rate of > 30 L/min, continuous positive airway pressure (CPAP), or bi-level positive airway pressure (BiPAP). The primary safety outcome will be major bleeding (author defined).

Search Strategy and Identification of Studies

Using the OVID platform, we will search MEDLINE® (including Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations), Embase and the Cochrane Central

Register of Controlled Trials (CENTRAL). Using individualized systematic search strategies for each database, we will identify relevant citations of studies from inception to August 2023. Search strategies will utilize a combination of controlled vocabulary (e.g.: "pneumonia", "pneumonia, bacterial", "pneumonia, viral", "aspirin") and keywords (e.g.: "pneumoni*", "antiplatelet*", "acetylsalicylic acid"). We will apply a modified version of the SIGN RCT and observational study filters.[30] We will not use language restrictions for any searches. The Medline search strategy is presented in **Appendix 2**. Reference lists of relevant narrative reviews, systematic reviews, and the included studies will be searched for additional citations. To identify planned, on-going, or recently completed but unpublished clinical trials, we will search clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP), and abstracts from relevant conferences. We will perform reference management in EndNote™ (Version 20.5, Thomson Reuters, Philadelphia, PA, USA).

Study Selection and Data Extraction

We will examine all citations produced from the search strategy and remove duplicate citations. We will screen all title and abstracts and select studies applying the eligibility criteria, recording all decisions using the Rayyan artificial intelligence web-based platform.[31] Full texts will be obtained for all citations that meet eligibility criteria, and these studies will be examined applying the inclusion and exclusion criteria, and the report of clinical outcomes. If full texts are not in the English language, we will translate with the online translator Google Translate (*United States, Google LLC*, 2016).[32,33] The included studies will then be reviewed for data extraction using standardized and piloted screening and data extractions forms in Microsoft®

Excel for Mac (version 16.69). Citations that cannot be excluded based on population, intervention, comparator, or study design will be moved to full text screening. Two reviewers will independently perform citation screening and full text screening, study selection, and data extraction in parallel. Conflicts between reviewers will be resolved by consensus or resolution of disagreements by a third reviewer as required.

From each study, we will extract study demographics including the study name, first author's name, study design, publication year, journal, publication type (full article or abstract), publication language, sources of funding (industry vs. non-industry), study locations (continent), and number of centers. We will record participant characteristics in respective intervention and control arms, including total sample size, mean or median age and sex, and proportion of patients with immunocompromising condition(s), chronic respiratory or cardiovascular conditions, and history of MI or coronary artery disease (author defined). Participant diagnoses will be recorded including pathogen type (proportion bacterial, viral, or unknown), and illness severity (proportion in ICU at enrolment, baseline Sequential Organ Failure Assessment (SOFA) and/or Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and/or Pneumonia Severity Index (PSI) and/or Confusion, Urea, Respiratory Rate, Blood Pressure-65 (CURB-65) score). We will record intervention characteristics, including the type of anti-platelet agent, total daily dose, proportion exposed to the anti-platelet agent prior to enrolment, whether the anti-platelet agent was started prospectively at the time of study enrolment, the duration of anti-platelet agent use after enrolment, and the proportion on concurrent therapeutic-dose anticoagulation. Lastly, we will record the duration of participant follow up and the outcomes

of interest. For missing data, we will email the corresponding author for studies that are < 10 years old. If no response is received within 1 months, a second contact will be made, after which the data will considered missing.

Risk of bias assessment

We will assess the internal validity at both the study and outcome level of included RCTs using the Cochrane Collaboration Risk of Bias tool (version 2).[34] This tool consists of 5 domains (bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result), and a categorization of the overall risk of bias. Each separate domain will be rated "low risk", "some concerns", or "high risk". The overall judgment will be low risk if all domains are judged to be low risk. The study will be judged as having some concerns, if at least one domain is judged to raise some concerns (but not at high risk of bias for any domain). Finally, the study will be judged as high risk if any one domain is judged high risk, or if the study is judged to have some concerns for multiple domains such that it substantially lowers the confidence in the results.

For observational studies, we will assess study quality using the Newcastle-Ottawa Scale (NOS).[35] This tool consists of assessing quality within a list of numbered items in 3 domains, based on the selection of the study groups (4 numbered items), the comparability of the groups (1 numbered item), and the ascertainment of the outcome of interest (3 numbered items). High quality choices within each numbered item will be awarded a "star" (maximum 1 star per

numbered item in the selection and outcome domains, maximum 2 stars for the numbered item in the comparability domain). Each study will be assigned a score of 0-9 stars. Studies scoring ≥ 7 will be considered high quality studies, 4-6 moderate quality, and ≤ 3 low quality.

Risk of bias assessment will be performed independently by two reviewers. Discrepancies between the two reviewers will be resolved by consensus or by resolution of conflicts by a third reviewer as required. Information regarding risk of bias will be used to guide sensitivity analyses and explore sources of heterogeneity.

Data analysis

Meta-analysis will be conducted using Random effect inverse variance model. In the primary meta-analysis of the primary outcome, study level adjusted mortality estimates from observational studies will be presented as hazard ratios (HR) and adjusted odds ratios (OR) and will be pooled separately. Study level summary effect comparisons from RCTs will be presented as risk ratios (RR) with 95% confidence intervals (CI) and pooled separately. A secondary meta-analysis of the primary outcome will be performed using study level unadjusted reported effect estimates and presented as RR with 95% CI. Reported OR will be converted back to RR before conducting meta-analysis. Summary effect-estimates for secondary outcomes will be expressed as RR with 95% CI for dichotomous data and weighted mean difference (WMD) with 95% CI for continuous data. Provided there are sufficient included studies (≥ 10) in the analysis of the primary outcome, a funnel plot will be used to investigate publication bias with the Egger test and visual inspection to assess plot asymmetry.[36,37] All analyses will be conducted using the

general meta and metafor package[38] in RStudio version 2023.09.1+494, R version 4.3.2 (R Project for Statistical Computing).

Assessment of Heterogeneity and Subgroup Analysis

The presence of statistical heterogeneity will be expressed using the I^2 statistic.[39] In case of significant heterogeneity among studies (I^2 > 50%) , we will perform pre-defined subgroup analyses for the primary outcome, dependent on the number of included studies and the availability of appropriate outcomes and co-variates. These will include subgroups from studies with potential differences in methodologic considerations, included study populations, pneumonia type, or disease severity, factors that relate to the intervention, or duration of follow up (**Table 3**).

Table 3: Pre-defined sub-group analyses

Methodological subgroups	• Cochrane risk of bias for RCTs (high vs. low) • Newcastle Ottawa scale study quality for observational studies (high vs. intermediate/low) • Sample size (large (n>1,500) vs. small (n≤1500) • Data source for pneumonia diagnosis (clinical vs. administrative data)
Clinical subgroups (based on population factors)	• Study population (entire study population with CAP vs. data generated in a subgroup of patients with CAP) • Etiology of CAP (bacterial vs. viral vs. unknown/mixed) • Illness severity (admitted to ICU at time of study enrollment vs. not in ICU)
Interventional subgroups	• Type of anti-platelet agent used (ASA vs. other anti-platelet agent) • Dose of ASA (high vs. low dose ≤ 81 mg/d) • Pre-hospital exposure to anti-platelet agent (chronic vs. new use of anti-platelet agent) • Duration of anti-platelet agent use (≤ 7 days vs. > 7 days)

Outcome subgroups	• Duration of follow up for the primary outcome (≤ 30 days vs. > 30 days)

External validity

We will apply the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework to summarize the strength of the evidence generated and make clinical practice recommendations.[40]

DISCUSSION

The findings generated in this systematic review and meta-analysis will be summarized and presented at local and national conferences concurrently with publication in a peer reviewed journal. The findings will be used to inform the relevance and potential study design for a future large, international RCT of anti-platelet agents in CAP. Planned future studies will be presented to the Canadian Critical Care Trials Group and other national organizations that include general internists (Canadian Society of Internal Medicine), infectious disease experts (Association of Medical Microbiology and Infectious Disease Canada), and critical care experts (Critical Care Canada Forum) to seek future collaborations.

ABBREVIATIONS

APACHE II Acute Physiology and Chronic Health Evaluation-II

APT Anti-platelet

ASA	Acetyl-salicylic acid
BiPAP	Bi-Level Positive Airway Pressure
CAP	Community Acquired Pneumonia
CI	Confidence Interval
COVID-19	Coronavirus Disease-19
CPAP	Continuous Positive Airway Pressure
CURB-65	Confusion, Urea, Respiratory Rate, Blood Pressure-65 score
DAPT	Dual Anti-platelet
ECLS	Extra-corporeal Life Support
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HFNO	High Flow Nasal Oxygen
HR	Hazard Ratio
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive Care Unit
IMV	Invasive Mechanical Ventilation
LOS	Length of Stay
LRTI	Lower Respiratory Tract Infection
MI	Myocardial Infarction
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NIPPV	Non-Invasive Positive Pressure Ventilation

NOS	Newcastle Ottawa Scale
OR	Odds Ratio
PICO	Population Intervention Comparators and Outcomes
PRISMA	Preferred Reporting items for Systematic Reviews and Meta-analysis
PSI	Pneumonia Severity Index
RCT	Randomized Controlled Trial
RR	Risk Ratio
SOFA	Sequential Organ Failure Assessment
URTI	Upper Respiratory Tract Infection
VTE	Venous Thromboembolism
WMD	Weighted mean difference

DECLARATIONS

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Search strings will be published in the included appendix. Data that is generated from extraction of included studies will be published in a peer reviewed journal and raw data will be publicly available on Open Science Forum or upon request with the corresponding author.

Competing interests: The authors declare that they have no competing interests

Funding: No sources of funding

Author contributions: Each author contributed to creating, editing, and approving the final draft of this manuscript. Individual roles of each co-author is detailed in Appendix 1.

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APPENDIX

Appendix 1: Systematic review team members

The review will be coordinated by a clinician scientist with infectious diseases and critical care training (SL), including development of the review question, literature search strategy, screening of relevant studies, data extraction and analysis, and preparation of the final manuscript. A second blinded reviewer (LT) with internal medicine training will screen relevant studies, extract data, and analyze risk of biases in duplicate. Experts from a variety of fields will provide content expertise, including infectious diseases (YK, AK, SM), critical care (AK, PL, AM, BR, SM, JM, AT, RZ), hematology and thrombosis (BH, RZ, EM, DH), cardiology (PL), community health and epidemiology (SS), and knowledge synthesis methodology (AMAS, NA, RR, YK, PL, SS, SM, JM, AT, RZ). An experienced librarian and medical information specialist with experience in systematic review search methodology will develop and test search strategies through an iterative process in consultation with the review team (NA). Another information specialist will peer review the search strategies prior to execution using the PRESS Checklist.[41] A senior statistician with specific expertise in meta-analysis will oversee the analysis methods (RR). A clinician scientist with systematic review expertise in clinical trials and prospective observational studies (AMAS) will provide methodological advice. Two clinician scientists with expertise in infectious diseases, hematology and critical care will provide project oversight, methodological advice, along with content expertise, and resolution of disagreements among reviewers (YK, RZ).

Appendix 2: Search strategy for Medline (Ovid)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to August 22, 2023>

1	Platelet Aggregation Inhibitors/ or exp Anti-Inflammatory Agents, Non-Steroidal/	243981
2	exp aspirin/ or abciximab/ or ancrod/ or cilostazol/ or clopidogrel/ or dipyridamole/ or disintegrins/ or epoprostenol/ or eptifibatide/ or exp heparitin sulfate/ or iloprost/ or pentoxifylline/ or piracetam/ or prasugrel hydrochloride/ or ticagrelor/ or ticlopidine/ or tirofiban/ or aminosalicylic acid/ or exp aminopyrine/ or apazone/ or benzydamine/ or clonixin/ or diclofenac/ or Diflunisal/ or dipyrone/ or Epirizole/ or Etanercept/ or Etodolac/ or etoricoxib/ or Fenoprofen/ or Feprazone/ or exp fenamates/ or Flurbiprofen/ or ibuprofen/ or Indomethacin/ or Indoprofen/ or Ketoprofen/ or ketorolac/ or Ketorolac Tromethamine/ or Nabumetone/ or naproxen/ or Piroxicam/ or exp Salicylates/ or Sulindac/ or Suprofen/ or Tolmetin/	197866
3	(antiplatelet* or anti platelet* or antithrombocyt* or anti thrombocyt* or antiaggrega* or anti aggrega* or nsaid* or nsaia*).ti,ab,kf.	73353
4	((nonsteroid* or non-steroid* or analgesic*) adj2 (antiinflammat* or anti inflammat*)).ti,ab,kf.	51370
5	((platelet* or thrombocyte* or cyclooxygenase* or cyclo oxygenase* or prostaglandin synth* or prostaglandin endoperoxide or cox or cox1 or cox2 or adp receptor* or adenosine or glycoprotein or gpii* or thromboxane or fibrinogen receptor* or thrombin receptor or thromboxan*) adj2 (inhibit* or antagonist*)).ti,ab,kf.	62091
6	(acenterine or acesal or acetan or acetard or acetic#l or acetilum or acetonyl or acetophen or ac#tosal* or acetylsalic* or acetyl* salic* or acetylin or acetylo* or acety?sal or actorin or acylpyrin* or adiro or aggrenox or alabukun or alasil or aloxiprimum or anadin or anasprin or anopyrin or asaphen or asasantin* or ascriptin or aspercin or aspica or aspir or aspirem or aspirgran or aspiricor or aspirin* or aspirisucre or aspirlow or aspirtab or aspisol or asprin or aspro or axanum or axotal or bisospirine or boxazin or breoprin or buffasal or bufferin or buffinol or calcacetosal or calspirin or calsprate or cardiprin or cardioasa* or cardio?spirina or casprin or caspirin or catalgix or colfarit or concorasa or coryphen or curilen or decagesic or dispirin or dispril or duocover or duoplavin or durlaza or easprin or ecosprin or ecotrin or empirin or endosprin or entaprin or enteroprin or enterosarine or enterospirine or entrophen or eskotrin or eudorlin or euthermine or extren or fasprin or globentyl or halfprin or idotyl or invagesic or istopirin or ivepirine or juvepirine or kalmopyrin or kinderaspirin or magnecyl or medaprin or mejoral or melabon or meproaspirin or methoxisal or micrainin or micristin or miniprin or nitroaspirin or norgesic or novasen or orphengesic or ostoprin or pabaxin or planolar or poloprin or polopiryna or premaspin or primaspan or rasprin or regasprin or renolon or rhonal or rivasa or robaxisal or rumarid or salacetin or salicyla* or salicylic or sedergine or solprin or solupsan or svelux or syna?gos or tevapirin or trancoprin or trinomia or tycalsin or uniprin or vazalore or vicoprin or vosprala or zactrin or zorprin).ti,ab,kf.	95704
7	(aloxiprin or alaprin or palaprin or paloxin or rumatral or superpyrin or tiatral or anagrelide or agrelid or agrelin or anegrilide or xagrid or ancrod or viprinex or agkistrodon or applaggin or aprosulate or aspalatone or ataprost or atopaxar or beraprost* or buflomedil or pirxane or cangrelor or kengreal or kengrexal or	83521

	caplacizumab or cablivi or cicaprost or cilostazol or aggravan or cilental or cilostad or cilostop or cilotal or claudiasil or decilosal or dilsatan or ekistol or pladizol or silosta or soliazon or sollazon or trastocir or ciprostene or clopidogrel or clopilet or myogrel or plavitor or plavix or pregrel or zylagren or cryptolepine or dazoxiben or dehydrocilostazol or dipyridamole or adezan or agremol or antiplate or aponova or atlantin or atrombin or cardoxin or chilcolan or cleridium or coronair or coronamole or corosan or curant#l or dip#ridamol* or dipyramidole or dipyridamide or dypyrol or efosin or gulliostin or isephanine or persantine or justpertin or miosen or perazodin or peridamol or persantin* or persantione or posanin or prandiol or prespex or prexin or procardin or pyranistole or pyridantin or ridamol or rupenol or solantin or tovincocard or trolactin or trompersantin or vasokor or elinogrel or enfenamic acid or tromaril or esuberaprost or abciximab or centorx or albolabrin or bitistatin or carafiban or contortrostatin or disintegrin* or echistatin or elarofiban or eptifibatide or integr#lin or intrifiban or fradafiban or gantofiban or kistrin or lamifiban or lefradafiban or lotrafiban or orbofiban or roxifiban or lumaxis or sibrafiban or tadocizumab or tirofiban or aggrafiban or aggrast#t or agrastat or triflavin or trigramin or xemilofiban or xemlofiban or zalunfiban or glenzocimab or heparan* or heparitin or ifetroban or iloprost or calovat or ciloprost or endoprost or ilomedin* or ventavis or imolamine or angolon or indobufen or ibustrin or isbogrel or itazigrel or itazogrel or linotroban or lixazinone or mipitroban or nafazatrom or naxaprostene or octimibate or oxagrelate or pht?alazinol or pamicogrel or pentoxifylline or agapurin or azupentat or azutrenat or carpental or ceretal or claudicat or elorgan or erytal or fixoten or flexital or hemovas or ipentol or kentadin or oxpentifylline or penphylline or pentopak or pentox* or perencal or perental or peridane or ralofe#t or relofe#t or tarontal or rentylin or thrental or torental or torestal or trenlin or vazofen or picotamide or plactidil or piracetam or avigilen or cerebroforte or cerebrosteril or ciclofaline or cuxabrain or durapitrop or encetrop or euvifor or gabacet or memopuren or noostan or nootron or nootropil or nootropyl or novocetam or oikamid or piracetan or piracetrop or piramem or pirazetam or pyracetam or pyramem or plafibride or perifunal or plafibrinol or prasugrel or effient or prostacyclin or caripul or cycloprostin or epoprostenol or veletri or ventaprost or rafigrelide or regrelor or samixogrel or sarpogrelate or anplag or satigrel or selatogrel or taprostene or temanogrel or terbogrel or terutroban or vorapaxar or zontivity or ticagrelor or brilinta or ticlopidine or agulan or anagregal or antigreg or aplaket or cartrilet or cenpidine or clotidone or licodin or nufaclapide or panaldine or ticlid or ticlodine or ticlodone or tilodene or viladil or treprostinil or orenicell or orenileft or orenitram or remodulin or treposuvi or uniprost or yutrepia or triflusal or trombodipine).ti,ab,kf.	
8	(aceclofenac* or rantudil or alclofenac or medifenac or zumaril or alminoprofen or mina?f?ene or amfenac or butapyrine or irgapyrin* or aminosalicyl* or aminacyl or ampiroxicam or amtolmetin*or atliprofen or bakeprofen or benor#lat* or benoxaprofen* or bermoprofen or dibenon or bromfenac or carbasalate or redupsan or solup#an or carprofen or c#cloprofen or cinmet?acin or indolacin or clidanac or clofenamic or clonixin* or dorixin* or cloximate or deracoxib or dexibuprofen or seractil or dexketoprofen or ketodex or dexpemedolac or diclofenac or algoplast or almiral or berifen or clonodifen or cordralan or curinflam or declophen or diclac or diclax or diclo or diclophenac or dicrofenac or dichlofenal or diclonate or dolotren or feloran or voltaren or voltarol or novapirina or orthofen or ortofen or orthophen or zolterol or motusol or arthrotec or artotec or miclofenac or diclopram or medinac or	106653

	cataflam or diflunisal or dolobid or dolocid or nudiflunisal or novodiflunisal or apodiflunisal or ditazol* or droxicam or ombolan or duometacin or flynpovi or endolac or epirizole or mep#rizole or vimovo or etanercept or etodolac or ecridoxan or etodolic or ramodar or ultradol or etofenamate or algesalone or etophenamate or etoricoxib or arcoxia or duexa or daitac or felbinac or fenamate* or fenamic or fenbufen or fenclofenac or fenclozic or fendosal or alnovin or fenflumizol* or fen?profen or fenopron or trandor or fentiaza* or feprazone or flobufen or flufenam* or fluphenam* or dignodolin or flunoxaprofen or fluproquazone or flurbiprofen* or flurbiproben or ansaid or cebutid or ocufen or flugalin or nitroflurbiprofen* or fosfosal or furaprofen or enprofen or furcloprofen or furofenac or glucamet?acin* or teorem* or codofen or vicoprofen or ibufenac or ibuprofen or advil or ibumetin or motrin or salprofen or algifast or dolomate or dolormin or fidiprofen or ibalgin or nurofen or comb#nox or combogesic or cetafen or dolerin or fidiprofen or ibuprom or ibutren or ibuvalen or modafen or sinuphen* or ibuproxam or ilonidap or flogozen or indameth* or indomet* or algometacin or osmosin or indocin or liometacen or indoprofen or dexindoprofen* or isoxicam or kebuzone or racheton or ketazon or phloguron or copirene or ketoprofen or artrosilene or ketorolac or toradol or tromedal or acular or licofelone or lobuprofen or lonazolac or lornoxicam or losmiprofen or loxoprofen or loxonin or lumiracoxib or prexige or mabuprofen or meclofenam* or meclophenam* or meclomen or medofenam* or mefenam* or numefenam* or contraflam or pontal or ponstan or mefacit or pinalgesic or ponalar or ponalgic or apomefenam* or met?iazin* or met?oxibutropate or flubenil or milategrast or microprofen or mofebutazone or mobutazon or mofezolac or nabumeton* or aponabumeton* or arthraxan or relafen or nabucox or naproxen* or aleve or napros#n or anaprox or proxen or synflex or trexima or treximet or nepafenac or nevanac or neurofenac or ni#tindol* or niflumi* or nimesulide or odalprofen or orpanoxin or oxamet?acin or indoxamic or oxaprozin or dan#prox or oxicam or oxinda#ac or pelubiprofen or pemedolac or piketoprofen or pimeprofen or piproxen or pirproxen or numidan or p#razolac or piroxicam or feldene or brexicam or pir?profen or r#angasil or pranoprofen or proglumetacin or tolindol or protacin* or proquazone or sulindac or aposulin or sulin or clinoril or klinoril or sulindal or kenalin or novosundac or nusulindac or suprofen or maldocil or procofen or profenal or sutoprofen or tenoxicam or reutenox or artriunic or tilcotil or t?iaprofen* or surgam or tiaramide or tilnoprofen or tioxaprofen or tolfenam* or tolfedine or tolmetin* or tolectin or tropesin* or repanidal or valerylsalicyl* or vedaprofen or quadrisol or ximoprofen or zaltoprofen or soreton or soleton or zidometacin* or zomepirac*).ti,ab,kf.	
9	(aminophenazon* or aminofenazon* or amidophen or aminopyrine or dipurine or amidazophen or eufibron or ampyrone or aminoantipyrine or apazone or prolixan or tolyprin or azapropazone or benz#damine or bumadizone or eumotol or quarelin or strexate or carsalam or cholisate or clomet?acin* or duperan or mindolic or dipyron* or met?amizol* or biopyrin or novalgetol or novalgin or pyralgin or sulpyrin* or novamidazophen or methampyrone or algopyrin or analgin or narone or normelubrine or nolotil or et?enzamide or glycosalicyl* or tifurac).ti,ab,kf.	7490
10	or/1-9	466553
11	pneumonia/ or bronchopneumonia/ or pleuropneumonia/ or exp pneumonia, bacterial/ or pneumonia, necrotizing/ or pneumonia, pneumocystis/ or pneumonia, viral/ or pulmonary eosinophilia/	135323

12	community-acquired infections/	15998
13	respiratory tract infections/	42843
14	influenza, human/ or exp influenzavirus A/ or exp influenzavirus B/ or influenzavirus C/ or streptococcal infections/ or pneumococcal infections/ or Streptococcus pneumoniae/ or Streptococcus pyogenes/ or Respiratory Syncytial Virus, Human/ or Respiratory Syncytial Virus/ or pneumovirus/ or metapneumovirus/ or exp pneumovirus infections/ or Mycoplasma pneumoniae/ or Mycoplasma Infections/ or Paramyxoviridae Infections/ or Parainfluenza Virus 2, Human/ or Parainfluenza Virus 4, Human/ or Respirovirus Infections/ or respirovirus/ or Parainfluenza Virus 1, Human/ or Parainfluenza Virus 3, Human/ or Legionnaires' Disease/ or Legionella pneumophila/ or rhinovirus/ or common cold/ or Adenovirus Infections, Human/ or Adenoviruses, Human/ or Herpesviridae Infections/ or chickenpox/ or Herpesvirus 3, Human/ or Epstein-Barr Virus Infections/ or Herpesvirus 4, Human/ or Chlamydophila pneumoniae/ or Chlamydophila Infections/ or Psittacosis/ or Klebsiella pneumoniae/ or Klebsiella Infections/ or exp Haemophilus influenzae/ or Haemophilus Infections/ or measles/ or Measles virus/ or Whooping Cough/ or Bordetella pertussis/ or Moraxella catarrhalis/ or Moraxellaceae Infections/ or Staphylococcus aureus/ or Staphylococcal Infections/ or exp Rickettsiaceae Infections/ or exp Rickettsieae/ or exp bronchitis/ or Pseudomonas aeruginosa/ or Pseudomonas Infections/ or Yersinia pestis/ or exp Yersinia Infections/ or Coxiella burnetii/ or Q fever/ or Severe acute respiratory syndrome-related coronavirus/ or Severe Acute Respiratory Syndrome/ or Middle East Respiratory Syndrome Coronavirus/ or Coronavirus Infections/ or Hantavirus Infections/ or exp Orthohantavirus/ or Rubella/ or Rubella virus/ or Cytomegalovirus Infections/ or Cytomegalovirus/ or exp Dengue/ or dengue virus/ or Coccidioidomycosis/ or Coccidioides/ or Pneumocystis Infections/ or Pneumocystis/ or Aspergillosis/ or exp Pulmonary Aspergillosis/ or exp Aspergillus/ or Histoplasmosis/ or histoplasma/ or toxoplasma/ or Toxoplasmosis/ or tularemia/ or Francisella tularensis/ or Paracoccidioidomycosis/ or Paracoccidioides/ or Blastomycosis/ or Blastomyces/ or Coxsackievirus Infections/ or Enterovirus B, Human/ or candidiasis/ or exp candida/ or Escherichia coli Infections/ or Escherichia coli/ or Actinomycosis/ or Actinomyces/ or Nocardia Infections/ or exp Nocardia/	1090059
15	sepsis/ or exp bacteremia/ or exp fungemia/ or shock, septic/ or parasitemia/ or exp viremia/ or respiratory distress syndrome/ or acute lung injury/ or pulmonary atelectasis/	176986
16	(pneumoni* or bronchopneumoni* or pleuropneumoni* or peripneumoni* or lobitis or loeffler* or loffler* or carrington* or weingarten* or bronchoalveolit* or lung fever* or cavitary necrosis or (bronch* adj2 (vesicular* or capillar* or suffocativa)) or (tropic* adj2 eosinophil*) or ((pulmon* or lung* or bronch* or lobe or lobular or lobar or multilob*) adj2 (inflamm* or infiltrat* or eosinophil*))).ti,ab,kf.	269526
17	((communityacquir or communityassociat* or ((acquir* or associat*) adj3 communit*)) adj3 infect*).ti,ab,kf.	5763
18	(urti$1 or lrti$1 or ((respiratory or bronchial or broncho* or bronchus or pulmonary or airway* or tracheobronch*) adj2 (infect* or mycosis))).ti,ab,kf.	82941
19	(influenza* or flu or flus or grippe or h1n1 or h2n2 or h3n2 or h5n1 or h7n7 or h7n9 or streptococc* or pneumococc* or pyogenes or scarlatinae or rsv or (respiratory adj2 syncytial) or respirosyncytial* or rs virus or pneumovir* or orthopneumovir* or pneumo vir* or metapneumovir* or paramyxovir* or eaton or lyopneumoni* or	1666229

	mycoplasm* or parainfluenza* or rubula or rubulavir* or respirovir* or pneumophil* or legionnair* or legionell* or veteran* disease or rhinovir* or common cold or cold virus or coryza or adenovir* or mastadenovir* or hadv or herpes virus or herpetovir* or herpesvir* or chicken pox or chickenpox or varicell* or alphaherpesvir* or betaherpesvir* or epsteinbarr or epstein barr or lymphocryptovir* or chlamydophil* or chlamydi* or chlamidi* or ornithosis or psittacosis or psittaci or klebsiell* or friedla?nder or pneumobacill* or hyalococc* or haemophilus or hemophilus or pfeiffer* or measles or rubeola or morbilli or morbillivir* or rougeole or whooping cough or pertussis or bordetell* or abettin or tussis or tussisconvulsivae or catarrh* or moraxella* or psychobacter* or staph or staphylococc* or aureus or mrsa or mssa or orsa or vrsa or vssa or rickettsi* or scrub typhus or orientia or tsutsugamushi or bronchiti* or bronchioliti* or boop or laryngotracheiti* or laryngotracheobronchiti* or tracheobronchiti* or aeruginos* or pyocyane* or blue pus or pseudomona* or yersinia* or pestis or yersinosis or plague or pestilential fever or burneti* or coxiella or q fever or coxiellosis or derrickburnet* or derrick burnet* or nine mile fever or queensland fever or query fever or sars or severe acute respiratory syndrome or sars-cov-1 or sudden acute respiratory syndrome or Middle East Respiratory Syndrome or mers or merscov or hantavir* or muerto canyon or orthohantavir* or rubella or rubivir* or cmv or hcmv or cytomegal* or dengue or aden fever or bouquet fever or breakbone fever or break bone fever or solar fever or sun fever or denv or coccidiod* or immitis or posadasii or coccidiomycosi* or pneumocyst* or carini* or jirovecii or aspergillosis or aspergillus or fumigatus or histoplasm* or cave disease or darling* disease or ajellomyces or capsulatu* or posadasia or toxoplasm* or gondii or tular?emi* or deerfly fever or deer fly fever or tularens* or francisella or lemming fever or ohara* disease or yato by* or yatoby* or paracoccidiod* or lutz splendore almeida or blastomy#osis or blastomyces or gilchrist* or coxsackie* or enterovir* or echovir* or echo vir* or candidiasis or candida or candidamyco* or monilia* or candidosis or torulopsis or escherichia or e coli or colibacill* or coliform or ((bacill* or bacteri*) adj2 coli) or actinomyc* or nocardia* or nocardiosis or nocarida).ti,ab,kf.	
20	(sepsis* or septic* or bacter?emi* or bacill?emi* or fung?emi* or candid?emi* or toxic forward failure or (shock adj2 (toxic or endotoxi* or bacteri* or lung)) or py?emi* or pyoseptic* or phyohemi* or parasit?emi* or vir?emi* or (distress syndrome* adj2 (lung or pulmonary or breath* or respiratory)) or rds or ards or (acute* adj2 (lung* or pulmonary or respiratory) adj2 (injur* or distress or failure)) or adult respirat* distress or ((post trauma* or posttrauma* or collapse*) adj2 (lung* or pulmonary or respirat* or alveol*)) or diffus* alveol* damage* or atelectasis).ti,ab,kf.	332643
21	or/11-20	2337520
22	exp "clinical trials as topic"/ or randomized controlled trial/ or random allocation/ or double blind method/ or single blind method/ or clinical trial/ or placebos/	1329569
23	(clinical trial phase iii or clinical trial phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.	1157417
24	((clinical adj trial*) or ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)) or placebo* or (random* adj2 allocat*) or randomi?ed).tw.	1245413
25	epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or cross-sectional studies/	3141222
26	observational study.pt.	145169

27	(case control or (cohort adj (study or studies or analy*)) or ((followup or follow up or observational) adj (study or studies)) or longitudinal or prospective or crosssection* or cross section*).tw.	1975089
28	or/22-27	5415915
29	(biography or case reports or comment or editorial or interview or letter or news or newspaper article or review or meta analysis or systematic review).pt.	7908032
30	exp animals/ not humans.sh.	5148283
31	(adolescent/ or exp child/ or exp infant/) not exp adult/	2146405
32	28 not (29 or 30 or 31)	3950729
33	10 and 21 and 32	2099

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4**:1**

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5**:15**

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	72
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	35-38
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	125-129; 468-486
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes;	☐	☒	NA

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		otherwise, state plan for documenting important protocol amendments			
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	349
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	77-118
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	114-118; 131-133, Table 1
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	138-139, 145-167, Table 2
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	185-188
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	188-199
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	202-214
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	211-214
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done	☒	☐	216-234

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		independently, in duplicate), any processes for obtaining and confirming data from investigators			
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	216-232
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	169-183
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	236-256
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	263-286, Table 3
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	263-286
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	279-286, Table 3
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	273-275
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	291-294

501
502

8.2 Study 1 manuscript

Lother SA, Tennenhouse LG, Rabbani R, Abou-Setta AM, Askin N, Turgeon AF, Murthy S, Houston BL, Houston DS, Mendelson AA, Paul JD, Farkouh ME, Hasmatali J, Rush B, Nkosi J, Goligher EC, Rimmer E, Marshall JC, Shaw SY, Lawler PR, Keynan Y, Zarychanski R. The association of antiplatelet agents with mortality among patients with non-COVID-19 community acquired pneumonia: A systematic review and meta-analysis. *Res Pract Thromb Haemost*. Jul 2024; S2475-0379(24)00221-8

The association of antiplatelet agents with mortality among patients with non-COVID-19 community-acquired pneumonia: A systematic review and meta-analysis

Authors:
Sylvain A. Lother[1,2], Lana Tennenhouse[3], Rasheda Rabbani[4], Ahmed M. Abou-Setta[4,5], Nicole Askin[6], Alexis F. Turgeon[7,8], Srinivas Murthy[9], Brett L. Houston[10,11], Donald S. Houston[10,11], Asher A. Mendelson[2], Jonathan D. Paul[12], Michael E. Farkouh[13], Jovan Hasmatali[2], Barret Rush[2], Joel Nkosi[3], Ewan C. Goligher[14], Emily Rimmer[10,11], John C. Marshall[15], Souradet Y. Shaw[5], Patrick R. Lawler[16,17], Yoav Keynan*[1,5,18], Ryan Zarychanski*[2,10,11]

Affiliations:
1 Section of Infectious Diseases, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
2 Section of Critical Care, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
3 Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
4 George & Fay Yee Centre for Healthcare Innovation, University of Manitoba, Winnipeg, Manitoba, Canada
5 Department of Community Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
6 Neil John Maclean Health Sciences Library, University of Manitoba, Winnipeg, Manitoba, Canada
7 Department of Anesthesiology and Critical Care, Université Laval, Quebec City, Quebec, Canada
8 Population Health and Optimal Health Practices Research Unit, Departments of Traumatology, Emergency Medicine, and Critical Care Medicine, Université Laval Research Center, CHU de Quebec-Université Laval, Quebec City, Quebec, Canada
9 Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada
10 Department of Medical Oncology and Hematology, CancerCare Manitoba, Winnipeg, Manitoba, Canada
11 Section of Hematology and Medical Oncology, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
12 Section of Cardiology, Department of Medicine, University of Chicago Medical Center, Chicago, Illinois, USA
13 Academic Affairs, Cedars-Sinai Health System, Los Angeles, California, USA
14 Interdepartmental Division of Critical Care Medicine, and the Department of Medicine and Physiology, University of Toronto, Toronto, Onatrio, Canada
15 Departments of Surgery and Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada
16 University of Toronto, Toronto, Ontario, Canada
17 McGill University Health Centre and McGill University, Montreal, Quebec, Canada
18 Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada
*Co-senior authors

Corresponding author: Dr. Sylvain A. Lother
University of Manitoba, Health Sciences Center
GC 436, 820 Sherbrook St, Winnipeg, MB, R3A1R9
+1-(204)-787-2767, Sylvain.Lother@umanitoba.ca
@sylvainlother

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Abstract

Background: Community-acquired pneumonia (CAP) triggers inflammatory and thrombotic host responses driving morbidity and mortality. Antiplatelet agents may favorably modulate these pathways; however, their role in non-COVID-19 CAP remains uncertain.

Objective: To evaluate the association of antiplatelet agents with mortality in hospitalized patients with non-COVID-19 CAP.

Methods: We conducted a systematic review and meta-analysis of observational studies and randomized controlled trials (RCTs) of adult patients hospitalized for non-COVID-19 CAP exposed to antiplatelet agents (ASA or P2Y12 inhibitors). We searched MEDLINE, Embase, and CENTRAL from inception to August 2023. Our primary outcome was all-cause mortality; meta-analyzed (random-effects models) separately for observational studies and RCTs. For observational studies, we used adjusted mortality estimates.

Results: We included 13 observational studies (123,012 patients; 6 reported adjusted mortality estimates) and 2 RCTs (225 patients; both high risk of bias). In observational studies reporting hazard ratio (HR), antiplatelet agents were associated with lower mortality (HR 0.65, 95% CI 0.46-0.91; I^2 85%; 4 studies, 91,430 patients). In studies reporting adjusted odds ratio (OR), antiplatelet agent exposure was associated with reduced odds of mortality (OR 0.67, 95% CI 0.45-1.00; I^2 0%; 2 studies, 24,889 patients). Among RCTs, there was a non-significant association with mortality (risk ratio 0.66, 95% 0.20-2.25; I^2 54%; 2 studies, 225 patients). By GRADE criteria, the certainty of the evidence was low, primarily due to risk of bias.

Conclusions: In hospitalized patients with non-COVID-19 CAP, antiplatelet agents may be associated with reduced mortality compared to usual care or placebo, but the certainty of evidence is low.

Key words

Aspirin, clopidogrel, infection, mortality, pneumonia

Essentials

- Pneumonia is a lung infection that increases inflammation and clotting
- We analyzed studies of antiplatelet drugs in hospitalized patients with non-COVID pneumonia
- Antiplatelet agents may be associated with reduced mortality in patients with pneumonia
- Included studies were at high risk of bias, and the certainty of the findings was low

Introduction

Community-acquired pneumonia (CAP) is a leading cause of hospitalization and mortality globally.[1,2,3] Inflammatory and thrombotic host responses contribute to end-organ dysfunction through micro and macro-vascular thrombosis.[4,5] Cardiovascular events complicate CAP in up to a third of hospitalizations,[6-8] and vascular thrombosis occurs in up to 11% of patients.[6,9,10]

Antiplatelet agents including acetylsalicylic acid (ASA) and P2Y12 inhibitors such as clopidogrel, prasugrel, and ticagrelor are widely accessible medications that have pleiotropic effects, including anti-thrombotic and anti-inflammatory activity.[11-13] These mechanisms may blunt maladaptive host responses to infection.[14]

ASA demonstrated no clinical benefits in trials of hospitalized patients with COVID-19 pneumonia at short durations of follow-up (< 30 days),[15-17] although there was a suggestion of a mortality benefit at longer follow up duration (180-days).[14] In non-COVID-19 CAP, a small randomized control trial (RCT) showed reduced acute coronary syndromes (ACS) and cardiovascular death in patients treated with ASA after hospitalization for CAP.[18] Several other retrospective and prospective cohort studies have suggested a potential benefit for antiplatelet agent exposure; however, because of disease and study heterogeneity, their overall effect in hospitalized patients with CAP remains uncertain.[19-21]

This systematic review and meta-analysis evaluates the association of antiplatelet agents with mortality, the need for organ support, and cardiovascular events in patients hospitalized with non-COVID-19 CAP.

Methods

Using an *a priori* published protocol,[22] we conducted a systematic review using methodological approaches outlined in the *Cochrane Handbook for Systematic Reviewers.*[23] Our review was reported following the Preferred Reporting items for Systematic Reviews and Meta-analysis (PRISMA).[24] The review question and methods were informed by experts in various specialties of medicine, knowledge synthesis, and research methodology. Screening, full-text review, data extraction, and quality assessment/risk of bias evaluation were performed in duplicate by independent reviewers who were blinded to each other's assessments. The roles of each team member are summarized in **Appendix 1**.

Populations, Interventions, Comparators and Outcome Measures

We included studies of hospitalized adults admitted for non-COVID-19 CAP that compared patients who did and did not receive an antiplatelet agent; we excluded studies of hospital acquired pneumonia (HAP) or ventilator associated pneumonia (VAP). Study designs included observational studies (retrospective and/or prospective) and RCTs; we excluded quasi-randomized trials and case-control studies. Antiplatelet exposure was defined as receipt of ASA or a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) at any dose or frequency after study enrollment. Studies that included patients with antiplatelet exposure prior study enrollment were included, regardless of the indication. Complete inclusion and exclusion criteria are listed in **Appendix 2, Table S1**.

Our primary outcome was all-cause mortality at longest follow-up. The primary safety outcome was author-defined major bleeding. Secondary outcomes measured at longest follow-up were

intensive care unit (ICU) admission, hospital length of stay, use of invasive mechanical ventilation (IMV), cardiovascular organ support, organ support (composite including use of high flow nasal oxygen (HFNO), non-invasive positive pressure ventilation (NIPPV), IMV, vasopressors, inotropes, or extracorporeal life support), and the incidence of arterial thrombosis or incidence of venous thromboembolism.

Search Strategy and Identification of Studies

Our search strategy (**Appendix 3**) was peer reviewed using the PRESS checklist.[25] Using the OVID platform, we systematically searched MEDLINE® (including Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to August 2023; we also searched clinical trial registries (clinicaltrials.gov, WHO International Clinical Trials Registry Platform). We applied a modified version of the SIGN RCT and observational study filters.[26] Reference lists of relevant reviews and included studies were searched for additional citations. Reference management was performed in EndNote™ (Version 20.5, Thomson Reuters, Philadelphia, PA, USA).

Study Selection, Data Extraction, and Risk of Bias Assessment

We screened citations applying eligibility criteria and recorded decisions using the Rayyan platform.[27] Data were extracted from included studies using standardized forms in Microsoft® Excel for Mac (version 16.69). From each study, we extracted study characteristics, intervention characteristics (including the type of antiplatelet agent, total daily dose, and the proportion exposed to the antiplatelet agent before enrolment), duration of participant follow-up, and

outcome data. We assessed the internal validity of included RCTs using the Cochrane Risk of Bias (RoB) tool (version 2).[28] For observational studies, study quality was assessed using the Newcastle-Ottawa Scale (NOS).[29] Information regarding RoB was used to guide sensitivity analyses and explore heterogeneity.

Data Analysis

Meta-analyses were conducted using random effect inverse variance models. In the meta-analysis of the primary outcome, study-level adjusted mortality estimates from observational studies were pooled and presented separately as adjusted hazard ratio (HR) and adjusted odds ratio (OR) with 95% confidence intervals (CI). Unadjusted study-level summary effect comparisons from RCTs were presented as risk ratios (RR) with 95% CI. Unadjusted summary effect estimates for secondary outcomes were expressed as RR with 95% CI for dichotomous data. Statistical heterogeneity was quantified using the I^2 statistic.[30] All analyses were conducted using the general meta and metafor package[31] in RStudio version 2023.09.1+494, R version, 4.3.2 (R project for Statistical computing). We used The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework to evaluate the strength of the evidence.[32]

Subgroup Analyses

Subgroup and sensitivity analyses were planned *a priori* for the primary mortality outcome. We performed subgroup analyses based on methodological factors (risk of bias), clinical factors (etiology of CAP and illness severity), intervention factors (type and dose of antiplatelet, pre-

hospital exposure to antiplatelet, and duration of antiplatelet intervention), and duration of study follow up.

Results

Trial Characteristics and Included Study Populations

Of the 7,696 citations identified, we included 15 unique studies: 13 observational studies (n=123,012)[33-45] and 2 RCTs (n=225)[46,47] (**Figure 1**). Of the observational studies, five (38%) were prospective,[34,35,37,38,42] eight (62%) retrospective,[33,36,39-41,43-45] and most (85%) were published in peer-reviewed journals (2 were abstracts from conference proceedings).[33,43] Sample sizes ranged in observational studies between 224 to 88,315 patients, and sample sizes in the two RCTs were 27 and 198 patients.[46,47] All studies were non-industry funded and published between 2008 to 2023. Studies were performed in Europe (53%),[34,35,37,39,42,44,45,47] North America (13%),[40,41], Oceania (7%),[33] Asia (7%),[36] or intercontinental (20%),[38,43,46] and most studies were multicenter (60%).[36,38-40,42-44,46,47]

The study level mean age was 70.1 (mean age within each study ranged from 59.9 – 76.7) years and the average proportion of females was 42% (**Table 1**). At baseline, the proportion of participants reported to have chronic respiratory diseases, cardiovascular diseases, and coronary artery disease was 28%, 26%, and 17%, respectively. Three observational studies reported inclusion of patients with immunocompromising conditions,[37,38,44] representing 4% of included patients. One observational study included only patients with confirmed bacterial CAP,[44] whereas all other studies did not report pathogen type. Three observational studies[36,38,41] and one RCT[47] included patients only with severe pneumonia.

Of the 13 included observational studies, seven (54%) were adjudicated to be of high quality,[35,37-41,44] three (23%) intermediate,[34,36,42] and three (23%) were of low quality.[33,43,45] Only six (46%) reported an adjusted effect estimate of the primary outcome to account for possible confounders.[35,37-40,44] Both included RCTs were determined to be at high risk of bias due to reporting unclear processes of randomization, allocation concealment, or lacking prespecified analysis plans.[46,47]

Exposures

Observational studies evaluated the effect of ASA (54%),[34,35,37-39,41,44] clopidogrel (8%),[40] or any antiplatelet (38%) exposure.[33,36,42,43,45] In studies that included any antiplatelet agent, most of the exposure was to ASA (**Table 1**). Dosing of ASA was reported in four studies and was predominantly low dose (≤100 mg/d).[34,37,38,45] All observational studies included patients with continued exposure to an antiplatelet agent that started before hospitalization. The comparator group in all studies received usual care (no antiplatelet agent), apart from one observational study which included a 2x2 comparison of exposure to ASA plus macrolide, ASA alone, macrolide alone, or usual care.[38] The largest RCT (n=198) randomized patients to ASA 300 mg/d vs. open-label usual care for up to 30 days,[46] and the second RCT (n=27) randomized patients to ASA 75 mg/d vs. placebo for up to 14 days.[47]

Primary outcome

Adjusted all-cause mortality summary effect estimates from observational studies were meta-analyzed by hazard ratio (**Figure 2**) or adjusted odds ratio (**Figure 3**). Results from RCTs were

pooled separately (**Figure 4**). Meta-analysis of observational studies reporting HR demonstrated an association between reduced risk of death and exposure to antiplatelet agents compared to usual care (HR 0.65, 95% CI 0.46-0.91; I^2 85%; 4 studies, 91,430 patients). In studies reporting adjusted OR, antiplatelet agent exposure was associated with reduced odds of dying over the study period (OR 0.67, 95% CI 0.45-1.00; I^2 0%; 2 studies, 24,889 patients). Using GRADE framework, the certainty of the evidence was low due to risk of bias in observational study designs, inconsistent effect estimates with heterogeneity in the pooled effect, and potential for publication bias (**Table 2**). In the 2 included RCTs (n=225 patients), the relative risk of all-cause mortality in patients randomized to receive ASA compared to usual care or placebo was 0.66 (95% 0.20-2.25; I^2 54%). The certainty of the evidence was low as both RCTs were at high risk of bias and due to imprecision in the effect estimates (**Table 2**).

Subgroup analyses for the mortality outcome reported in observational studies were conducted according to follow up duration, illness severity, study size, study quality and risk of bias, type of antiplatelet, study method for CAP diagnosis (clinical definition vs. administrative data set), and study source population (CAP study vs. CAP population derived from a larger sample). These were not associated with significant differences in treatment effect and did not reduce statistical heterogeneity (**Appendix 4, Figures S1-S7**). In the context of substantial between-study heterogeneity, sensitivity analyses were performed based on study differences which did not reduce heterogeneity. Funnel plot analysis was not performed due to the limited number of included studies. There was insufficient data available to conduct subgroup analyses according to dose, duration, or pre-hospital exposure to the antiplatelet agent.

Secondary Outcomes

As reported in a single RCT, ASA was not associated with an increased risk of bleeding, with no bleeding events reported in either the treatment or control group (n=185) (**Table 2**).[46] Antiplatelet agents were not associated with changes in ICU admission, use of IMV or organ support, or the incidence of myocardial infarction (author defined) (**Table 2**). One RCT reported a significant reduction in myocardial infarction in those randomized to aspirin compared to usual care (RR 0.10, 95% CI 0.01 – 0.79, 1 RCT, 185 patients)[46], however, the unadjusted pooled analysis from observational studies demonstrated no benefit (RR 6.69, 95% CI 0.16 – 271.55, n=1,997, 3 studies). Venous thromboembolic events and need for cardiovascular organ support outcomes were not reported from any of the included studies.

Discussion

In this systematic review and meta-analysis of studies that included patients hospitalized for non-COVID-19 CAP, we found that exposure to antiplatelet agents was inconsistently associated with reduced mortality compared to usual care or placebo. In observational studies, the exposure to an antiplatelet agent was associated with a 35% lower adjusted hazard of death. However, observational studies were of varying quality, and few reported adjusted outcome estimates. Among two small included RCTs, randomization to ASA was associated with non-significant reduction in the relative risk of mortality compared to usual care or placebo, although inferences were difficult to ascertain due to small sample sizes, low event rates, and considerable risk of bias. The GRADE certainty of evidence was low. We did not identify an increased risk of bleeding; however, this outcome was under-reported. Experience with ASA in hospitalized

COVID-19 patients would suggest an expected absolute increase in major bleeding events of 0.6-0.8%.[15,17]

Antiplatelet agents reduce complications associated with thromboinflammatory diseases such as coronary artery disease, stroke, and other thrombo-occlusive cardiovascular conditions.[48] Very limited data suggest that antiplatelet agents may also improve outcomes in acute infection. A meta-analysis of RCTs evaluating the effect of ASA in acute infections demonstrated reduced mortality (RR 0.44, 95% CI 0.24 – 0.81; 4 RCTs, 538 patients),[49] but only included one RCT of CAP patients.[46] In response to observations of increased thrombosis in COVID-19,[50] four RCTs evaluated antiplatelet agents in hospitalized COVID-19 patients demonstrating mixed results.[15,17,51,52] In the REMAP-CAP Bayesian adaptive platform trial (n=1,546), critically ill patients randomized within the antiplatelet domain had a 95% probability of improved 6-month survival (HR 0.85, 95% credible interval (CrI) 0.71 – 1.03).[14] In the RECOVERY trial (n=14,892), ASA was not associated with a reduction in mortality at 28 days (RR 0.96, 95% CI 0.89 - 1.04) or a difference in the proportion of patients who required ventilation or died (RR 0.96, 95% CI 0.90 – 1.03), but there was a significant reduction in thrombotic events (4.6 vs. 5.3%, absolute difference -0.6%, standard error 0.4%).[17] The COVID-PACT (n=292) and ACTIV-4a (n=1,549) trials did not demonstrate significant benefit with ASA or P2Y12 inhibitors.[15,51] The risk of major bleeding was small but increased among patients randomized to receive antiplatelet agents. In the context of inconsistent results in COVID-19, insufficient quality of evidence in other infections, and important unanswered questions (e.g., optimal type, dose, and duration of antiplatelet agents, impact of illness severity), antiplatelet agents are not currently recommended for the treatment of acute infections.[53] Although the mechanisms of

287 action differ, the promise of targeting thrombo-inflammation in CAP may be supported by the
288 observation that therapeutic-dose heparin improves outcomes in large RCTs of non-critically ill
289 patients with COVID-19.[54-59] None of the included studies reported patients receiving
290 anticoagulants, with or without an antiplatelet agent.
291
292 This systematic review builds on the evidence syntheses suggesting the possible benefit of
293 antiplatelet agents in CAP and other infectious syndromes. While we broadly included
294 observational studies of diverse CAP populations and illness severity, we also included studies of
295 bacteremia, sepsis, acute respiratory distress syndrome, and acute lung injury, where the effect of
296 antiplatelet agents was reported in CAP subgroups. The intent was to summarize the potential
297 comprehensive impact of antiplatelet agents in CAP; however, the calculated summary estimates
298 were associated with heterogeneity. Despite subgroup and sensitivity analyses, causes of
299 heterogeneity could not be fully resolved. Since effect summary estimates consistently favored
300 antiplatelet agents, unresolved heterogeneity could reflect uncertainty in the precise magnitude of
301 the effect, rather than presence or absence of efficacy. However, heterogeneity may also reflect
302 biases inherent to observational study designs or publication bias. Given the low certainty in the
303 findings, the true effect might be markedly different from the estimated effect.[32]
304
305 Due to widespread under-reporting of secondary outcomes, the analyses were largely limited to
306 unadjusted event rates from observational studies, with the potential for significant bias or
307 confounding, and thus very low certainty of the findings. As summarized in **Table 2**, we did not
308 find significant differences in any secondary outcomes associated with the use of antiplatelet
309 agents vs. usual care or placebo. The effect of antiplatelet agents on cardiovascular events is one

outcome of particular interest. Infection significantly increases the risk of in-hospital and post-discharge myocardial infarction (MI), but evidence regarding therapies to reduce such events is lacking.[7] In the largest of the included RCTs, ASA (300 mg/d) significantly reduced MI compared to usual care (RR 0.10, 95% CI 0.01 – 0.79, n=185).[46] The authors used a robust definition of MI, but the sample size and event rates were small, follow-up was short (30 days), and the open-label comparator could have introduced bias. If two more events were observed in the experimental arm, the findings would have been non-significant ($p > 0.05$, fragility index = 2). In contrast, the risk of MI was increased in the unadjusted pooled analysis from observational studies, with wide confidence margins and considerable potential for confounding. More studies are needed to understand the effect of antiplatelet agents on cardiovascular outcomes in patients with CAP.

Strengths

Our systematic review addresses an important knowledge gap and is the first to systematically summarize the evidence for antiplatelet agents in non-COVID-19 CAP. We utilized a comprehensive search strategy which included electronic databases, conference abstracts, trial registries, and forward searches following recognized methodologic guidelines for the conduct and reporting of systematic reviews, as outlined in our published protocol.[22] Our study outcomes were patient-centered and included the evaluation of safety related to the intervention (major bleeding). The broad inclusion of various CAP populations increases the generalizability of findings to a large population of CAP patients.

Limitations

The inclusion and substantive weighting of observational studies in systematic reviews of treatment effects confer risks due to imbalances between treatment groups and potential for confounding. Patients exposed to antiplatelet agents may have greater risks of experiencing the outcome with more comorbidities. However, receipt of antiplatelet agents may reflect better access to care, leading to more timely and effective infection treatments. Alternatively, control group patients may have unrecognized cardiovascular disease and may fair worse when not receiving antiplatelet agents. While we prioritized adjusted effect estimates from included observational studies, where available, potential confounding associated with the exposure and the outcome could not be excluded. Additionally, each study controlled for different covariates, and studies reported two different statistical methods to estimate measures of effect (HR and OR) which limited our ability to derive a single summary effect measure. Due to the insufficient number of studies reporting data on the type of antiplatelet, dose, and duration of use, meaningful subgroup analyses could not be conducted. The median duration of follow-up among included studies was short (67% of studies reported ≤30-day follow-up). Clinical outcomes measured at longer follow-up intervals could yield significantly different results given the pathobiology of inflammation and thrombosis in CAP where the risk of cardiovascular outcomes is increased for weeks to months post-discharge. It was not possible to assess for publication bias due to the small number of included studies. Finally, CAP and its respiratory sequelae are increasingly recognized to be heterogeneous conditions, with variable activation of inflammation between patients.[60] The study design could not consider such molecular heterogeneity of host response,[61] although it may bear consideration in future trials.[62]

Conclusions

In hospitalized patients with non-COVID-19 CAP, use of antiplatelet agents may be associated with reduced mortality compared to usual care or placebo, but the certainty of evidence is low. High quality RCTs are required to evaluate the potential clinical efficacy and safety of antiplatelet agents in CAP.

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Author Contributions

The review was coordinated by a clinician scientist with infectious diseases and critical care training (SL), including development of the review question, literature search strategy, screening of relevant studies, data extraction and analysis, and preparation of the final manuscript. A second blinded reviewer (LT) with internal medicine training screened relevant studies, extracted data, and analyzed risk of biases in duplicate. Experts from a variety of fields provided content expertise, including infectious diseases (YK, AK, SM), critical care (AK, PL, AM, BR, JH, EG, SM, JM, AT, RZ), hematology and thrombosis (BH, RZ, EM, DH), cardiology (JP, MEF, PL), internal medicine (JN), community health and epidemiology (SS), and knowledge synthesis methodology (AMAS, NA, RR, YK, PL, SS, SM, JK, JM, AT, RZ). An experienced librarian and medical information specialist with experience in systematic review search methodology (NA) developed and tested the search strategies through an iterative process in consultation with the review team. The search strategy was peer reviewed by a second independent information specialists using the PRESS Checklist.[25] A statistician with specific expertise in meta-analysis (RR) conducted the analyses in conjunction with the first author (SL) and in consultation with the review team. A clinician scientist with systematic review expertise in clinical trials and prospective observational studies (AMAS) provided methodological advice. Two clinician scientists with expertise in infectious diseases, hematology and critical care (YK, RZ) provided project oversight, methodological advice, along with content expertise, and resolution of disagreements among reviewers. All authors have had significant contribution to the above work and have reviewed and approved of this manuscript.

Open Practices Statement

The authors recognize the value of sharing results in the spirit of collaboration. Details of the methods were pre-registered on Open Science Framework on January 30, 2024 and are publicly available (DOI https://doi.org/10.17605/OSF.IO/H2G7C). The study materials (search strategies, analysis code) and data extracted can be made available upon request.

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Figure Legends

Figure 1. Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram[63]

Figure 2: Association of antiplatelet agents with mortality for observational studies reporting adjusted hazard ratios.

Figure 3: Association of antiplatelet agents with mortality for observational studies reporting adjusted odds ratios.

Figure 4 Association of ASA with mortality for RCTs reporting relative risk.

Tables

Table 1. Characteristics of individual trials, patient populations, and exposures

Study	Design	No. Patients APT/Control	Mean or median age	% female	% CAD	% CVD	% Severe CAP**	Type of APT (%)	Longest follow up (d)***
Bui 2022	Retrospective (conference proceeding)	117/336	72	52	22	NR	NR	Any APT (100) - Type NR	30
Cangemi 2014	Prospective	123/155	70	38	36	NR	NR	ASA (100)	NR
Chalmers 2008	Prospective	311/696	66	50	NR	20	NR	ASA (100)	30
Cilli 2018	Retrospective	111/262	68	42	NR	NR	100	Any APT (100) - ASA (74) - Alternative (26)	NR
Falcone 2015	Prospective	390/615	75	41	NR	31	NR	ASA (100)	30
Falcone 2019	Prospective	383/910	77	38	NR	26	100	ASA (100)	30
Gamst 2014	Retrospective (administrative data)	18,195/70,120	73	47	9	NR	7	ASA (100)	365
Gross 2013	Retrospective (administrative data)	2,908/20,974	NR	NR	NR	NR	NR	Clopidogrel (100)	NR
Lu 2023	Retrospective (administrative data)	182/580	NR	NR	NR	NR	100	ASA (100)	60
Nozzoli 2021	Prospective	455/811	76	49	17	NR	NR	Any APT (100) - Type NR	30
Peyrani 2016	Retrospective (Abstract)	639/2,698	NR	NR	NR	NR	NR	Any APT (100) - Type NR	30
Rognvaldsson 2022	Retrospective	128/687	67	48	17	NR	20	ASA (100)	365
Winning 2009	Retrospective	44/180	60	31	NR	NR	NR	Any APT (100) - ASA (86) - Clopidogrel (7) - Other (7)	28
Oz 2013	RCT	91/94	67	34	0	NR	NR	ASA (100)	30
Toner 2009	RCT	14/13	NR	NR	NR	NR	100	ASA (100)	90

APT = antiplatelet; C = control; CAD = coronary artery disease; CAP = community acquired pneumonia; CVD = cardiovascular disease; d = days; IQR = interquartile range; NR = not reported; SD = standard deviation

** Severe CAP was defined as a requirement for ICU admission for CAP

*** Longest follow-up for our primary outcome of mortality

Table 2: Results from meta-analyses including summary effect measures, number of participants, and certainty of evidence

Outcome	Relative effect Adjusted HR (95% CI)	Relative effect Adjusted OR (95% CI)	Relative effect Unadjusted RR (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)
Observational Studies					
Adjusted mortality**	0.65 (0.46 – 0.91)			91,430 (4 studies)	Low
		0.67 (0.45 – 1.00)		24,889 (2 studies)	Low
ICU admission			0.91 (0.79 – 1.03)	25,854 (4 studies)	Very low
Use of IMV			0.96 (0.59 – 1.56)	25,177 (2 studies)	Very low
Use of any organ support			1.54 (0.78 – 3.03)	2,755 (3 studies)	Very low
Myocardial infarction			6.69 (0.16 – 271.55)	1,997 (3 studies)	Very low
Randomized Controlled Trials					
Mortality**			0.66 (0.20 – 2.25)	212 (2 RCTs)	Low
Myocardial infarction			0.10 (0.01 – 0.79)	185 (1 RCT)	Very low
Bleeding			No events	185 (1 RCT)	Very low

aOR = adjusted odds ratio; APT = antiplatelet; HR = hazard ratio; ICU = intensive care unit; IMV = invasive mechanical ventilation; RCT = randomized controlled trial; RR = risk ratio

**Primary outcome and primary analysis

SUPPLEMENTARY MATERIALS

Supplementary Table: Eligibility criteria for studies to be included or excluded from the systematic review and meta-analysis

	Inclusion criteria	Exclusion criteria
Study design	RCTs (including placebo controlled and open label) and observational studies (including retrospective, prospective, and bi-directional cohort studies)	Animal studies, case-control studies, cross-over studies, cluster randomized trials
Participants	Comparative studies of adult patients admitted to a hospital for non-COVID-19 CAP (author defined), and studies of patients with bacteremia, sepsis, acute lung injury, and/or acute respiratory distress syndrome that report comparative effectiveness data for at least one clinical outcome in the CAP subgroup (derived CAP population with exposure to an APT vs. not)	Studies who enrol ≥ 20% of patients with URTI without evidence of LRTI, ≥ 20% with hospital acquired pneumonia (author defined), or ≥ 20% of CAP caused by COVID-19
Interventions	Studies where participants received ASA or a P2Y12 inhibitor, at any dose or frequency of administration, and regardless of whether the APT was received prior to hospitalization	Studies where ≥ 20% of patients are receiving DAPT, ≥ 20% of patients are receiving an APT in conjunction with therapeutic-dose anticoagulation
Comparator	Patients not receiving an APT (placebo, standard of care, no intervention, or another non-APT intervention)	Active comparator studies (one APT compared to another APT)
Outcomes	Primary outcome: • All-cause mortality (longest follow up) Secondary outcome: • ICU admission • Hospital LOS (days) • Use of IMV • Use of cardiovascular organ support (vasopressors and/or inotropes and/or ECLS) • Use of any organ support (composite including use of HFNO and/or NIPPV and/or IMV and/or vasopressors and/or inotropes and/or ECLS • Arterial thromboembolic event (myocardial infarction and/or stroke) • Venous thromboembolic event (deep venous thrombosis and/or pulmonary embolism) • Major bleeding	None of the listed outcomes are available from the study report(s) or through communication with the study authors
Setting	All hospital settings where patients with CAP are cared for	Patients cared for in personal care homes, long term care, or other non-hospital settings

APT = antiplatelet; ASA = acetyl salicylic acid; CAP = community acquired pneumonia; DAPT = dual antiplatelet; ECLS = extracorporeal life support; HFNO = high flow nasal oxygen; IMV = invasive mechanical ventilation; LOS = length of stay; LRTI = lower respiratory tract infection; NIPPV = non-invasive positive pressure ventilation; RCT = randomized controlled trial; URTI = upper respiratory tract infection

Supplementary Methods: Search strategy for Medline (Ovid)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to August 22, 2023>

1	Platelet Aggregation Inhibitors/ or exp Anti-Inflammatory Agents, Non-Steroidal/	243981
2	exp aspirin/ or abciximab/ or ancrod/ or cilostazol/ or clopidogrel/ or dipyridamole/ or disintegrins/ or epoprostenol/ or eptifibatide/ or exp heparitin sulfate/ or iloprost/ or pentoxifylline/ or piracetam/ or prasugrel hydrochloride/ or ticagrelor/ or ticlopidine/ or tirofiban/ or aminosalicylic acid/ or exp aminopyrine/ or apazone/ or benzydamine/ or clonixin/ or diclofenac/ or Diflunisal/ or dipyrone/ or Epirizole/ or Etanercept/ or Etodolac/ or etoricoxib/ or Fenoprofen/ or Feprazone/ or exp fenamates/ or Flurbiprofen/ or ibuprofen/ or Indomethacin/ or Indoprofen/ or Ketoprofen/ or ketorolac/ or Ketorolac Tromethamine/ or Nabumetone/ or naproxen/ or Piroxicam/ or exp Salicylates/ or Sulindac/ or Suprofen/ or Tolmetin/	197866
3	(antiplatelet* or anti platelet* or antithrombocyt* or anti thrombocyt* or antiaggrega* or anti aggrega* or nsaid* or nsaia*).ti,ab,kf.	73353
4	((nonsteroid* or non-steroid* or analgesic*) adj2 (antiinflammat* or anti inflammat*)).ti,ab,kf.	51370
5	((platelet* or thrombocyte* or cyclooxygenase* or cyclo oxygenase* or prostaglandin synth* or prostaglandin endoperoxide or cox or cox1 or cox2 or adp receptor* or adenosine or glycoprotein or gpii* or thromboxane or fibrinogen receptor* or thrombin receptor or thromboxan*) adj2 (inhibit* or antagonist*)).ti,ab,kf.	62091
6	(acenterine or acesal or acetan or acetard or acetic#l or acetilum or acetonyl or acetophen or ac#tosal* or acetylsalic* or acetyl* salic* or acetylin or acetylo* or acety?sal or actorin or acylpyrin* or adiro or aggrenox or alabukun or alasil or aloxiprimum or anadin or anasprin or anopyrin or asaphen or asasantin* or ascriptin or aspercin or aspica or aspir or aspirem or aspirgran or aspiricor or aspirin* or aspirisucre or aspirlow or aspirtab or aspisol or asprin or aspro or axanum or axotal or bisospirine or boxazin or breoprin or buffasal or bufferin or buffinol or calcacetosal or calspirin or calsprate or cardiprin or cardioasa* or cardio?spirina or casprin or caspirin or catalgix or colfarit or concorasa or coryphen or curilen or decagesic or dispirin or dispril or duocover or duoplavin or durlaza or easprin or ecosprin or ecotrin or empirin or endosprin or entaprin or enteroprin or enterosarine or enterospirine or entrophen or eskotrin or eudorlin or euthermine or extren or fasprin or globentyl or halfprin or idotyl or invagesic or istopirin or ivepirine or juvepirine or kalmopyrin or kinderaspirin or magnecyl or medaprin or mejoral or melabon or meproaspirin or methoxisal or micrainin or micristin or miniprin or nitroaspirin or norgesic or novasen or orphengesic or ostoprin or pabaxin or planolar or poloprin or polopiryna or premaspin or primaspan or rasprin or regasprin or renolon or rhonal or rivasa or robaxisal or rumarid or salacetin or salicyla* or salicylic or sedergine or solprin or solupsan or svelux or syna?gos or tevapirin or trancoprin or trinomia or tycalsin or uniprin or vazalore or vicoprin or vosprala or zactrin or zorprin).ti,ab,kf.	95704
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17	((communityacquir or communityassociat* or ((acquir* or associat*) adj3 communit*)) adj3 infect*).ti,ab,kf.	5763
18	(urti$1 or lrti$1 or ((respiratory or bronchial or broncho* or bronchus or pulmonary or airway* or tracheobronch*) adj2 (infect* or mycosis))).ti,ab,kf.	82941
19	(influenza* or flu or flus or grippe or h1n1 or h2n2 or h3n2 or h5n1 or h7n7 or h7n9 or streptococc* or pneumococc* or pyogenes or scarlatinae or rsv or (respiratory adj2 syncytial) or respirosyncytial* or rs virus or pneumovir* or orthopneumovir* or pneumo vir* or metapneumovir* or paramyxovir* or eaton or lyopneumoni* or mycoplasm* or parainfluenza* or rubula or rubulavir* or respirovir* or pneumophil* or legionnair* or legionell* or veteran* disease or rhinovir* or common cold or cold virus or coryza or adenovir* or mastadenovir* or hadv or herpes virus or herpetovir* or herpesvir* or chicken pox or chickenpox or varicell* or alphaherpesvir* or betaherpesvir* or epsteinbarr or epstein barr or lymphocryptovir* or chlamydophil* or chlamydi* or chlamidi* or ornithosis or psittacosis or psittaci or klebsiell* or friedla?nder or pneumobacill* or hyalococc* or haemophilus or hemophilus or pfeiffer* or measles or rubeola or morbilli or morbillivir* or rougeole or whooping cough or pertussis or bordetell* or abettin or tussis or tussisconvulsivae or catarrh* or moraxella* or psychobacter* or staph or staphylococc* or aureus or mrsa or mssa or orsa or vrsa or vssa or rickettsi* or scrub typhus or orientia or tsutsugamushi or bronchiti* or bronchioliti* or boop or laryngotracheiti* or laryngotracheobronchiti* or tracheobronchiti* or aeruginos* or pyocyane* or blue pus or pseudomona* or yersinia*	1666229

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29	(biography or case reports or comment or editorial or interview or letter or news or newspaper article or review or meta analysis or systematic review).pt.	7908032
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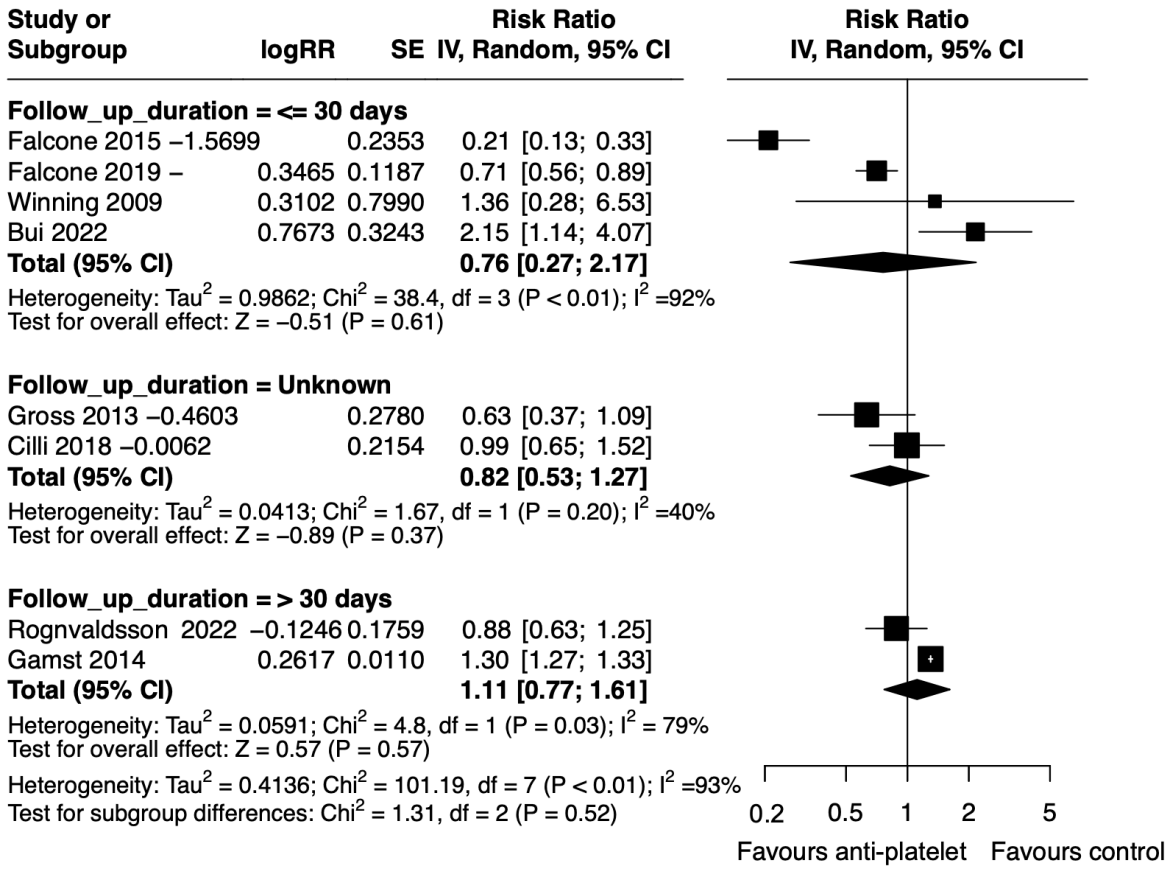
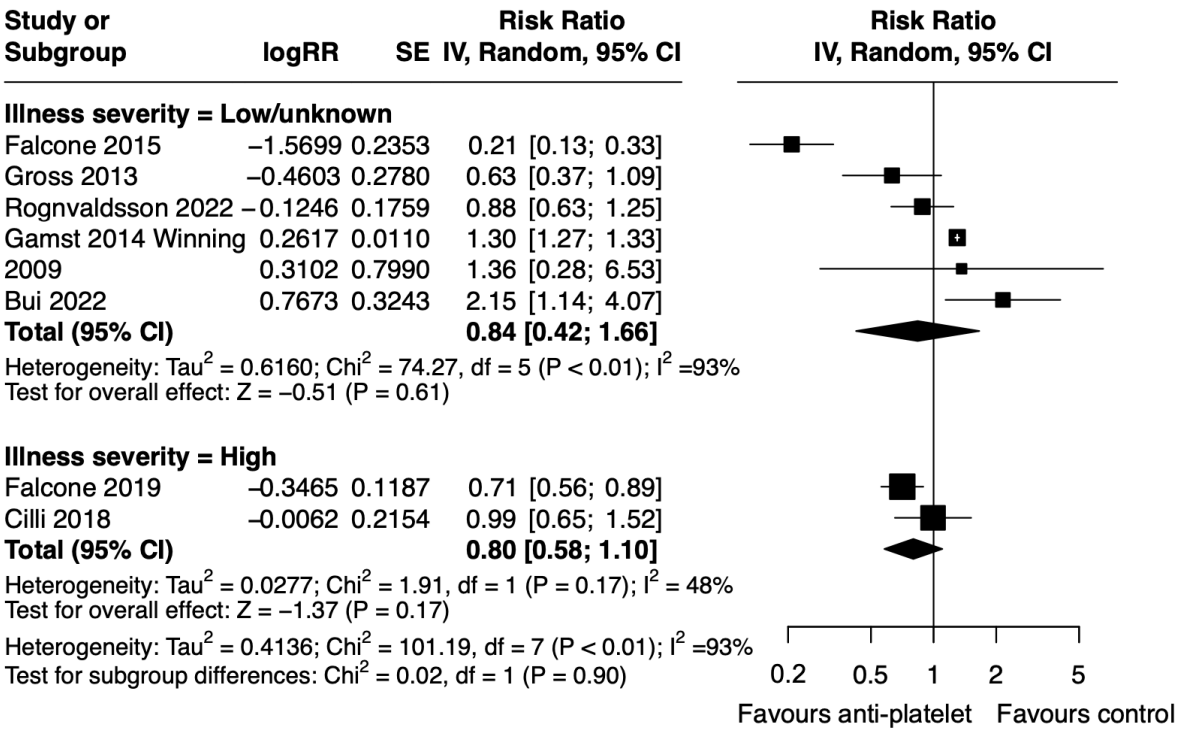
Supplementary Figures: Subgroup analyses for all-cause mortality in observational studies using unadjusted effect estimates

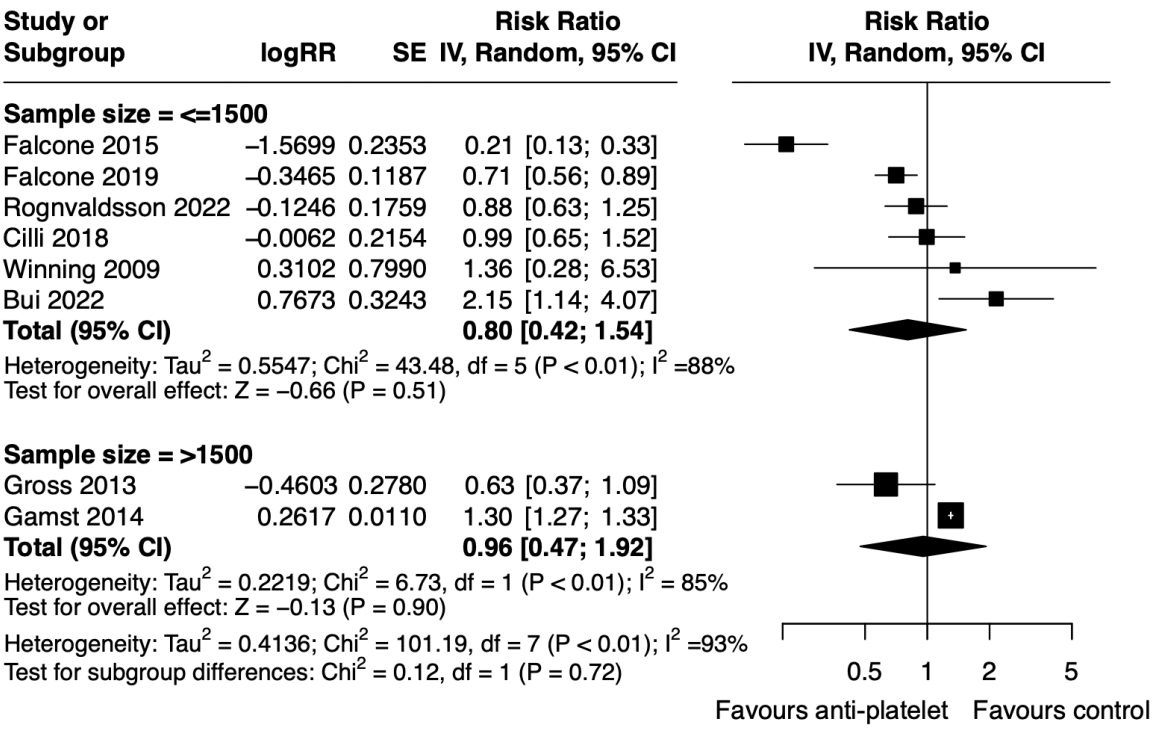
Supplementary Figure S1: All-cause mortality in observational studies by follow-up duration (≤30 days vs. unknown vs. > 30 days)



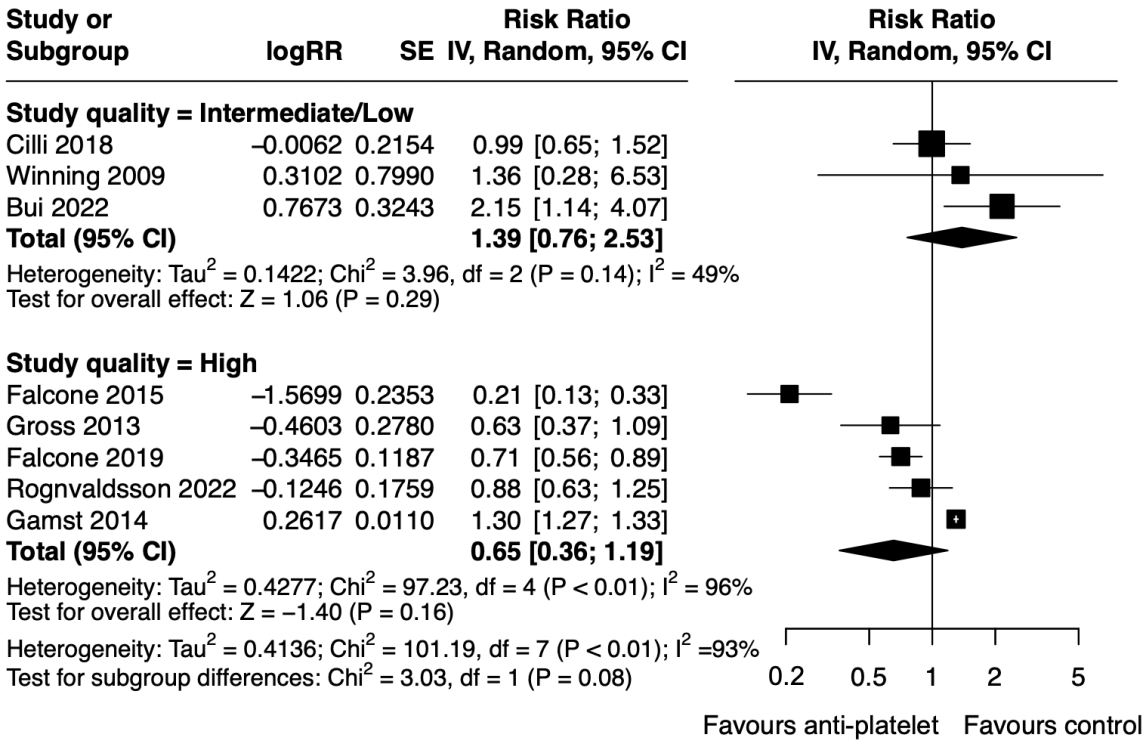
Supplementary Figure S2: All-cause mortality in observational studies by illness severity (high illness severity vs. low or unknown illness severity)



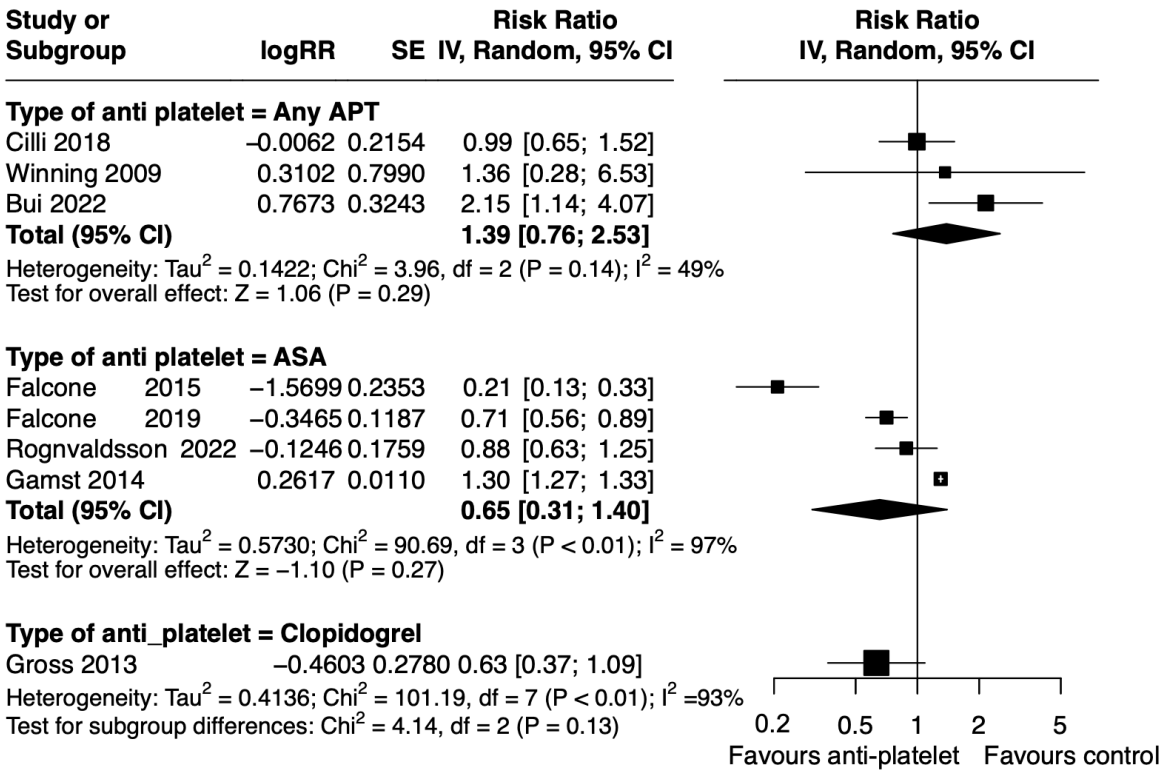
Supplementary Figure S3: All-cause mortality in observational studies by study size (sample size ≤ 1,500 patients vs. sample size > 1,500 patients)



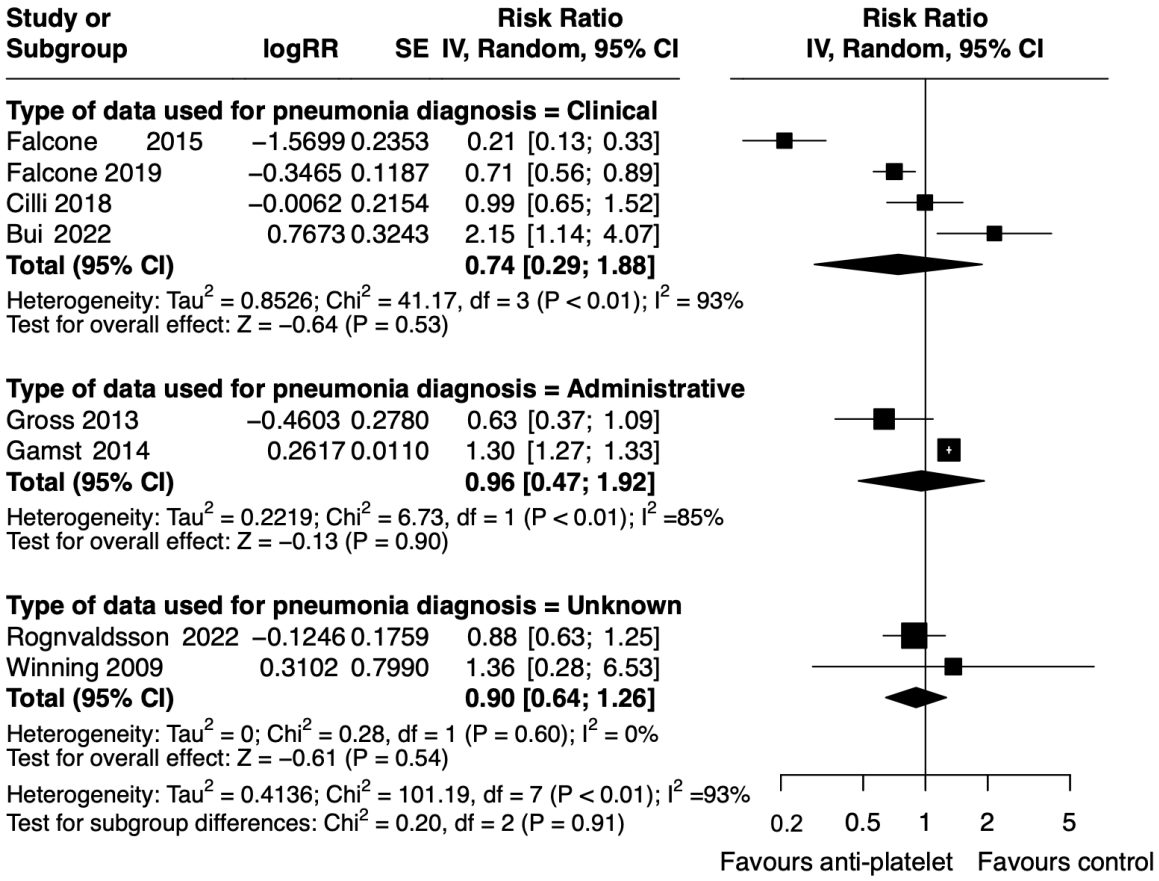
Supplementary Figure S4: All-cause mortality in observational studies by study quality (high quality vs. intermediate/low quality)



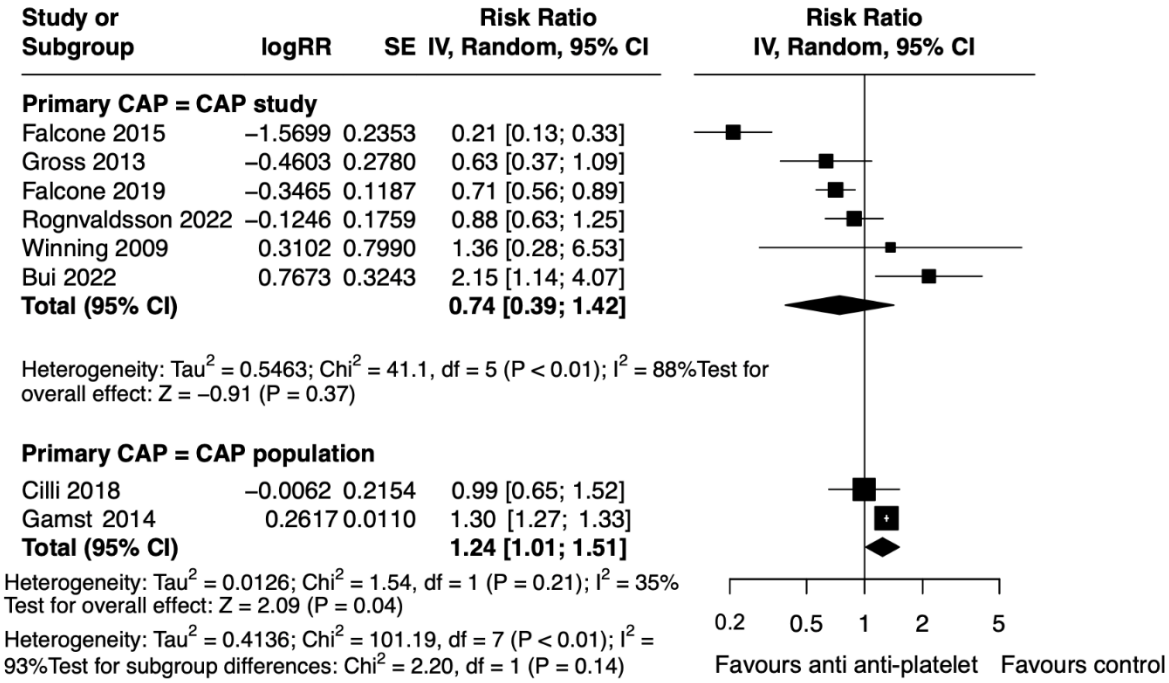
Supplementary Figure S5: All-cause mortality in observational studies by type of antiplatelet agent (any antiplatelet agent vs. ASA vs. clopidogrel)



Supplementary Figure S6: All-cause mortality in observational studies by method of CAP diagnosis (clinical definition vs. administrative data set definition vs. unknown)



Supplementary Figure S7: All-cause mortality in observational studies by study level population (study population with CAP only vs. CAP population derived from a larger study level population)



8.3 Study 2 statistical analysis plan

Lother SA. Therapeutic-dose heparin in combination with antiplatelet agents in non-critically ill patients hospitalized for COVID-19: A statistical analysis plan for a secondary analysis of the ATTACC and ACTIV-4a clinical trials. *Not submitted for publication*.

Therapeutic-dose heparin in combination with antiplatelet agents in non-critically ill patients hospitalized for COVID-19: A secondary analysis of the multiplatform randomized controlled trial

Statistical Analysis Plan

Version 1.1

Date: June 19, 2024

Author: Sylvain Lother

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1.0 Introduction

This statistical analysis plan (SAP) is to describe the methods and protocols for conducting a secondary analysis of the multiplatform randomized controlled trial (mpRCT). We will evaluate the combined treatment effect of therapeutic anticoagulation (TAC) with an antiplatelet agent (APT), including acetylsalicylic acid (ASA) or a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) among non-critically ill patients admitted to hospital for COVID-19. In this document, we outline the SAP for the exploration of treatment effect in patients receiving TAC + APT compared to those receiving TAC alone.

1.1 Background and rationale

COVID-19 has substantially increased global morbidity and mortality from pneumonia since the onset of the pandemic.[1] Poor clinical outcomes are driven by maladaptive inflammatory and thrombotic host responses to infection, leading to micro- and macro-vascular thrombosis and end-organ dysfunction.[2-4] In COVID-19 pneumonia, therapeutic interventions targeted at reducing host inflammatory and thrombotic responses have shown benefit, including anticoagulation with heparin and possibly also antiplatelet agents. Therapeutic-dose heparin reduces organ dysfunction and improves survival for non-critically ill patients hospitalized for COVID-19 and is now a guideline based treatment for COVID-19.[5] ASA, a well-known antiplatelet agent, has demonstrated mixed effects in COVID-19 clinical trials. Some trials demonstrated a benefit with ASA, others showed no significant effect.[6-8] A recent analysis suggested that, with longer follow up duration (180 days), ASA may reduce mortality.[9]

The cornerstone of therapy for other thromboinflammatory conditions such as myocardial infarction involves the combination of TAC + APT.[10] However, the effect of combination therapy on outcomes for infections driving thromboinflammatory conditions like COVID-19 has not been established.

1.2 Objective and hypothesis

The objective of this study is to examine the combined treatment effect of TAC + APT in non-critically ill patients admitted to hospital for COVID-19.

To investigate whether the combination of TAC + APT modifies the effect of TAC, we will evaluate the treatment effect of TAC + APT on survival without ICU-level organ support compared to enrolled participants who received TAC alone. We hypothesize that the combination of TAC + APT will lead to a greater treatment benefit than TAC alone.

2.0 Overall study design, setting, and population

2.1 Study design

The mpRCT was a large, multi-center, international trial conducted on multiple platforms with Bayesian adaptive stopping rules that enrolled critically ill and non-critically ill patients hospitalized for COVID-19. Patients were randomly assigned to receive TAC with either low molecular weight heparin or unfractionated heparin vs. standard of care. The treatment effect was analyzed separately in the critically ill (severe) and non-critically ill (moderate) patient populations and reported in simultaneous publications.[5,11] In the present study, we will conduct a retrospective propensity-adjusted secondary analysis of patients receiving TAC in the moderate (non-critically ill) stratum within the mpRCT dataset. **The primary analysis will estimate the effect of exposure to TAC + APT vs. TAC alone using a proportional odds model where the primary outcome is a composite ordinal outcome reflecting the need for ICU-level organ support and mortality.**

2.2 Population inclusion and exclusion criteria

All patients enrolled in the moderate illness severity stratum of the mpRCT who were randomized to receive TAC will be included (n=1,021).[5] The analysis will be limited to patients receiving TAC, since TAC is an effective and accepted standard treatment for COVID-19, and the primary objective of this study is to examine the combined treatment effect of TAC + APT compared to TAC alone. Patients within these trial platforms were defined as having moderate illness if they were hospitalized for COVID-19 but did not require ICU-level organ support at baseline (see 2.2.1/2.2.2 for inclusion/exclusion criteria). Patients were enrolled between April 21, 2020 to Jan 22, 2021.

A total of 194 patients concurrently, and non-randomly, received an APT in combination with TAC (**Table 1**).[5] The exposure to APT will be defined as at least one dose of ASA, or a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) given during hospitalization for COVID-19. The type of APT will be recorded and used for subgroup analyses (section 3.4). If more than one type of APT was used during the study, the first APT agent will be selected. Use of pre-hospital APT exposure will be recorded for sensitivity analyses (section 3.6). Patients receiving dual anti-platelet agents were excluded from the trial platforms (see section 2.2.2 for exclusion criteria).

Table 1: Use of antiplatelet agents by randomized treatment allocation

		Randomized treatment allocation
		TAC
Non-randomized exposure	APT	TAC + APT (n=194)
	No APT	TAC (n=827)

ATP, antiplatelet agent; TAC, therapeutic-dose anticoagulation with heparin

2.2.1 Inclusion

Inclusion criteria are as follows:

1) Adult patients aged (≥ 18 years), admitted to hospital for COVID-19
2) Moderately ill patients with laboratory confirmed COVID-19
    a. Moderately ill was defined as the absence of ICU-level organ support at the time of enrollment. ICU-level organ support was defined as the use of high flow nasal oxygen, non-invasive ventilation, invasive ventilation, extracorporeal life support, vasopressors, and/or inotropes delivered in an ICU or repurposed critical care area.

2.2.2 Exclusion

Exclusion criteria are as follows:

1) Patients who concomitantly received two or more antiplatelet agents (with the exception of ASA/dipyridamole, these patients were classified with patients receiving ASA)

2.2.3 Population flow diagram

A study flow diagram depicting enrollment, allocation, follow-up, and analysis will be created with the following information:

- Number enrolled in the ATTACC & ACTIV-4a platform
    - Reasons for exclusion (not meeting inclusion criteria, meeting an exclusion criteria)
- Number randomized to an anticoagulation strategy (TAC vs. VTP)
    - Number randomized to VTP
    - Number randomized to TAC
        - Number receiving TAC alone
        - Number receiving TAC + APT

2.3 Treatment groups

2.3.1 Intervention group

TAC + APT: Patients randomized to receive systemic therapeutic-dose anticoagulation with unfractionated or low molecular weight heparin PLUS exposure to an antiplatelet agent during hospitalization for COVID-19. Therapeutic-dose anticoagulation was administered according to local practice algorithms or guidelines for the treatment of venous thromboembolism.

2.3.2 Control group

TAC: Patients randomized to receive systemic therapeutic-dose anticoagulation with heparin WITHOUT exposure to an antiplatelet agent.

2.4 Main predictor

Exposure to an APT in the treatment group (TAC + APT) will be the main predictor and compared to the control group (TAC alone).

2.5 Endpoints

2.5.1 Primary endpoint

The primary endpoint will be the same composite ordinal outcome reported in the mpRCT – an ordinal endpoint reflecting survival to hospital discharge without ICU-level organ support in the first 21 days following randomization. This ordinal outcome has three levels:

A. Best: Survival without ICU-level organ support (alive at day 21, and never on organ support up to day 21)
B. Intermediate: Survival with organ support (alive at day 21, received organ support for any number of days to day 21)
C. Worst: Dead at day 21

ICU level organ support is defined as the use of high flow nasal oxygen (HFNO), non-invasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV), extracorporeal life support (ECLS), vasopressors, and/or inotropes delivered in an ICU or repurposed critical care area.

2.5.2 Secondary endpoints

Secondary endpoints, the types of variables, and their definitions are itemized in **Table 2**.

Table 2: Secondary endpoints

#	Endpoint	Variable type	Description	Notes
Components of the composite primary outcome				
2.1	Survival without ICU-level RS support	Ordinal	Ordinal outcome with 3 possible outcomes based on the worst status of each patient through day 21 a) Survival without HFNO, NIMV or IMV (without RS support) b) Survival with HFNO, NIMV or IMV (with RS support) c) Death	Will exclude patients who were on HFNO at baseline (~4%)
2.2	Survival without IMV	Dichotomous	Survived up to day 21, without requirement for IMV for any number of days within the first 21 days	1 – no IMV and survived 0 – otherwise
Other secondary outcomes				
2.3	90-day mortality	Dichotomous	Dead at 90 days	1 - death up to day 90 0 – otherwise
2.4	Hospital free days	Ordinal	Number of days alive and not admitted to hospital within the first 28 days	range from -1 to 28, where -

				1 indicates death during the first 28 days
2.5	Total thrombosis	Dichotomous	Any thrombotic event (arterial: systemic arterial embolization, stroke, or MI; or venous: DVT or PE) during hospitalization up to day 28	1 – thrombotic event 0 – otherwise
2.6	Major bleeding	Dichotomous	Experienced a major bleeding event on or before day 14	1 – bleeding event 0 – otherwise
2.6.1	Transfusion of ≥ 2 units of pRBC	Dichotomous	Number of participants requiring ≥ 2 units of pRBC transfusion to day 14	1 – yes 0 – no

DVT = deep venous thrombus; HFNO = high-flow nasal oxygen; IMV = invasive mechanical ventilation; MI = myocardial infarction; NIMV = non-invasive mechanical ventilation; OS = organ support; PE = pulmonary embolism; RBC = red blood cells; RS = respiratory

2.6 Study variables

Study variables included for descriptive and analytic purposes will include the following:

- Study factors: Country of enrolment (Brazil, Canada, US, UK, other), platform (ATTACC, ACTIV4a)
- Demographics: Age, sex (M/F), race (White, Asian, Black, First Nations or American Indian, Other), ethnicity (Hispanic or Latino, not Hispanic or Latino), body mass index (BMI)
- Comorbidities: Cardiovascular disease, diabetes, hypertension, chronic kidney disease (with or without dialysis), liver disease, chronic respiratory disease, immunosuppressive disease
    - Cardiovascular disease will be defined as a history of congestive heart failure (CHF), myocardial infarction (MI), coronary artery disease (CAD), peripheral arterial disease (PAD), or cerebrovascular disease (stroke or transient ischemic attack)
- Clinical presentation: Oxygen support at baseline (none, low-flow, high-flow, NIV)
- Lab values: Baseline d-dimer, platelet count, creatinine
- Treatment variables: Use of concurrent treatment for COVID (remdesivir, glucocorticoid, tocilizumab), use of pre-hospital antiplatelet treatment, type of anticoagulant and antiplatelet used

3.0 Statistical Analyses

3.1 Baseline comparison of treatment groups

Baseline characteristics will be summarized as mean with standard deviations or medians with interquartile ranges (for continuous variables) and proportions (for categorical variables). Standardized differences will be used to compare baseline characteristics between the two treatment groups (**Table 3**).

Table 3: Baseline characteristics of patients exposed and unexposed to anti-platelet drugs in patients randomized to receive TAC in the ATTACC and ACTIV-4a datasets before and after propensity score weighting

	Entire cohort			Post stabilized IPTW			
Variable*	TAC + APT (n=XX)	TAC alone (n=XX)	SD	TAC + APT (n=XX)	TAC alone (n=XX)	SD	% Reduction
Age (years), mean (SD)							
Female sex (%)							
Race (%)							
White							
Asian							
Black							
Indigenous							
Ethnicity (%)							
Hispanic or Latino							
BMI, mean (SD)							
Comorbidities (%)							
Immunosuppression							
CVD							
Respiratory disease							
Diabetes							
Hypertension							
CKD							
Co-treatment (%)							
Remdesivir (%)							
Corticosteroids							
Tocilizumab							
Oxygen support (%)							
No oxygen							
Low flow oxygen							
High flow oxygen							
Lab values, mean (SD)							
D-dimer (ULN)							
Platelets (x 10^9)							
Creatinine (mg/dL)							
Country of enrollment (%)							
Brazil							
Canada							
United States							

*Continuous variables are represented by mean (standard deviation); dichotomous variables are presented as %
APT = antiplatelet; BMI = body mass index; IPTW = inverse probability of treatment weighting; SD = standardized difference; TAC = therapeutic-dose anticoagulation

3.2 Propensity score

3.2.1 Propensity score estimation

A propensity score to estimate the patient's probability of receiving APT given their baseline characteristics will be created. Propensity scores will be estimated using a logistic regression model controlling for patient characteristics that are associated with the APT exposure and the primary outcome (see **Table 4)**. This model will be referred to as the ***treatment model***. An assessment to evaluate the overlap of propensity score distributions between treatment groups (TAC + APT vs. TAC alone) will be displayed visually using a histogram plot (**Figure 1**).

Table 4: Logistic regression propensity score model for APT use in patients randomized to receive TAC in the ATTACC and ACTIV-4a datasets

Covariate	Description	Odds ratio	95% CI
Age in years	Continuous variable		
Sex	Male	Reference	
	Female		
Race	White	Reference	
	Asian		
	Black		
	First Nations		
	Unknown		
Ethnicity	Not Hispanic/Latino	Reference	
	Hispanic/Latino		
	Unknown		
BMI	< 18.5	Reference	
	18.5 – 24.9		
	25 – 29.9		
	30 – 34.9		
	35 – 39.9		
	> 40		
	Unknown		
Immunosuppression	Absent	Reference	
	Present		
Cardiovascular disease	Absent	Reference	
	Present		
Respiratory disease	Absent	Reference	
	Present		
Diabetes	Absent	Reference	
	Present		
Hypertension	Absent	Reference	
	Present		
CKD	Absent	Reference	
	Present		
Baseline O2	No O2	Reference	
	Low-flow O2		
	High-flow O2		
	Unspecified		
D-dimer	Low	Reference	
	High		
	Unknown		
Creatinine	Continuous variable		
Platelet count	Continuous variable		
Corticosteroid treatment	No	Reference	
	Yes		
Remdesivir treatment	No	Reference	

	Yes		
Country of enrolment	Canada	Reference	
	Brazil		
	USA		

BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease

Figure 1*: Histogram distribution of propensity scores between treatment group and controls. The x-axis will display the distribution of propensity scores, and the y-axis the proportion (%). The treatment group will be labelled in blue, the control group labelled in red.*

3.2.2 Stabilized inverse probability of treatment weighting

Inverse probability of treatment weighting uses weights from propensity scores to create a ***pseudo-population***, to adjust for confounding and improve balance of the distributions of covariates in the treated and untreated groups. Each patient is assigned a weight equal to the inverse of their propensity score. Treated subjects with very small propensity scores (close to 0), and untreated subjects with large propensity scores (close to 1) may then be assigned a large weight with significant influence. To minimize undue influence from patients with extreme propensity scores, we will use stabilized IPTW (**Figure 2**).[12] We will consider the stabilized IPTW as the primary treatment model, as it uses most of the available patient data.

Figure 2: Methods to calculate stabilized IPTW

$$w_{i,treated} = \frac{1}{ps_i} \qquad w_{i,control} = \frac{1}{(1 - ps_i)}$$

w: IPTW; *ps*: propensity score

$$sw_{i,treated} = \frac{\Pr(X = 1)}{ps_i} \qquad sw_{i,control} = \frac{(1 - \Pr(X = 1))}{(1 - ps_i)}$$

sw: stabilized IPTW

ps: propensity score

Pr(X=1): marginal probability of treatment in the overall sample (i.e. overall mean of the propensity score)

3.2.3 Stabilized inverse probability of treatment weighting diagnostics

To evaluate the ability of the propensity weighting to balance observed covariates across treatment groups, standardized differences in means (in continuous covariates) or proportions (in dichotomous covariates) will be calculated (**Table 3**), graphically presented, and visually compared (**Figure 3**).[13] An absolute standardized difference < 0.1 will be used as a threshold for adequate covariate balance.[14] A cloud-plot figure will be displayed demonstrating the distribution of stabilized IPTW weights between the treatment group and control (**Figure 4**).

Figure 3: *Graphical representation of standardized differences in means or proportions of covariates between the treatment group (TAC + APT) and control (TAC alone). Standardized differences will be reported on the x-axis, and the covariates on the y-axis. The standardized*

differences in the unweighted cohort will be labelled in red, and the standardized differences in the weighted cohort in blue. Solid bars will be displayed at -0.1 and 0.1 indicating the range of appropriate covariate balance.

Figure 4: *Cloud-plot of the distribution of stabilized IPTW weights between the treatment group (TAC + APT) and control (TAC alone). The stabilized IPTW weight will be displayed on the x-axis, the treatment group (TAC + APT) and control (TAC alone) will be presented in their own column along the y-axis.*

Diagnostics for the stabilized IPTW weights will be reported with a mean stabilized weight (+/- standard deviation), and range. Diagnostics are important to determine whether conditioning on the estimated propensity score has removed observed systematic differences. A mean stabilized weight far from 1, or extreme values will suggest non-positivity or misspecification of the propensity score.

3.3 Analytic model for the primary endpoint

The primary analytic model will be a proportional odds model to estimate the effect of exposure to an antiplatelet agent on the primary outcome. This model will be referred to as the ***outcome model***. The only variable included in the primary analysis using the outcome model will be the treatment exposure (exposure to an antiplatelet). To control for residual confounding, additional variables may be included in the outcome model (see **section 3.6**). Effect comparisons will be presented as odds ratios (OR), where an OR of > 1 represents greater odds of a better outcome. The presentation of the primary outcome is summarized in **Table 5**.

Table 5: Estimate of the treatment effect for the primary outcome* in propensity weighted individuals in the treatment group (TAC + APT) vs. control group (TAC alone).

Outcome	TAC + APT	TAC alone	OR	95% CI	p-value
Survival to hospital discharge without ICU-level organ support	XX %	XX %			

APT = antiplatelet; CI = confidence interval; ICU = intensive care unit; OR = odds ratio; TAC = therapeutic-dose anti-coagulation

*Proportion of patients that survived to hospital discharge without the need for ICU-level organ support

3.4 Subgroup analyses

Sub-group analyses will be reported as summarized in **Table 6**. Reporting on any specific subgroup will depend on the number of subjects within that subgroup and completeness of data capture for that variable.

Table 6: Subgroup analyses of the effect of TAC + APT vs. TAC alone on the primary outcome* after propensity weighting

Category	Subgroup	OR (95% CI)
Age (years)	<50	
	50-70	
	>70	
Sex	Female	
	Male	
Race	White	
	Asian	
	Black	
	Indigenous	
	Hispanic or Latino	
	Other	
BMI (kg/m^2)	Underweight (<18.5)	
	18.5-29.9	
	Obese (≥30)	
Cardiovascular disease	No	
	Yes	
CKD	No	
	Yes	
Baseline oxygen support	None	
	Low-flow	
	High-flow	
	Ventilated	
	Unspecified	
D-dimer subgroups	Low	
	High	
	Missing	

*Number of patients that survived to day 28 without organ support
BMI = body mass index; CKD = chronic kidney disease; CI = confidence interval; OR = odds ratio

3.5 Analyses of secondary outcomes

We will use proportional odds models for ordinal outcomes and binary logistic regression models for dichotomous outcomes for each of the listed secondary outcomes (**Table 7**). An odds ratio (OR) of > 1 indicates a better outcome favoring the treatment group (TAC + anti-platelets).

Table 7: The effect of exposure to an antiplatelet agent on secondary outcomes in patients receiving therapeutic-dose heparin

Secondary outcome	**TAC + APT**	**TAC alone**	**OR**	**95% CI**	**p-value**
Survival to hospital discharge without ICU-level RS support (%)					
Survival to hospital discharge without need for IMV (%)					
90-day mortality (%)					
Hospital free days (days)					
Total thrombosis (%)					
Major bleeding events (%)					
Transfusion of ≥ 2 RBC units (%)					

APT = antiplatelet; CI = confidence interval; ICU = intensive care unit; IMV = invasive mechanical ventilation; OR = odds ratio; RBC = red blood cell; RS = respiratory; TAC = therapeutic anticoagulation

3.6 Sensitivity analyses

The goal of propensity methods is to create a pseudo-population where treatment and control groups are as similar as possible in measured covariates and differ only in the exposure to the treatment variable (exposure to an antiplatelet agent). However, propensity methods are imperfect at balancing all possible confounders, so we anticipate that our propensity analysis using stabilized IPTW may not eliminate all observed systematic differences between the treatment and control groups. There may be residual imbalance of certain covariates in the primary model, and thus confounding of the estimated treatment effect. To reduce residual confounding, we will perform sensitivity analyses. To enhance the performance of our propensity model, we will explore the effect of adjusting for potential non-linear relationships between certain covariates and the treatment exposure (ex: age) to evaluate if between group differences are improved (standardized differences < 0.1) (see **section 3.6.1**). For covariates that remain imbalanced (standardized differences > 0.1), we will explore the impact of adding these residual potential confounders into the outcome model (see **section 3.6.2**).

Furthermore, alternative propensity methods (matching and/or stratification) may perform differently in their ability to balance covariates, relative to weighting. We will compare the performance of these alternative methods in their ability to balance covariates between treatment groups and compare the influence of different propensity methods on the treatment effect estimate using propensity weighting, matching, and stratification (see **section 3.6.3**).

3.6.1 Improving between group balance in covariates in the pseudo-population by adjusting for non-linear relationships between covariates and the treatment exposure

Should certain covariates have non-linear relationships with the treatment exposure, there may be significant on-going between group differences in the pseudo-population distribution of such covariates (standardized differences > 0.1) using a linear regression analysis for the treatment model. To improve balance in these covariates, we will adjust for non-linearity within the treatment model to create a new pseudo-population. Diagnostics to determine whether conditioning on the estimated propensity score has removed observed systematic differences will be performed (as in **section 3.2.3**). The outcome model will be run using the newly generated stabilized IPTWs after controlling for non-linearity.

3.6.2 Adding additional covariates to the outcome model using stabilized IPTW

Should the pseudo-population created using stabilized IPTW be left with significant imbalance in covariates which may influence the treatment estimate in the primary outcome model, we will perform sensitivity analyses by adding covariates (with residual standardized differences > 0.1) to the outcome model. Content experts will guide which covariates to be included if they are felt to be clinically important and could exert residual confounding on the treatment effect. The estimated treatment effect and the direction of the effect will be compared to the primary model.

3.6.3 Alternative propensity methods – matching and stratification

We will perform propensity matching and stratification to create new pseudo-populations and compare the diagnostics of such methods to propensity weighting. Diagnostics to determine whether conditioning on the estimated propensity score has removed observed systematic differences will be performed (as in **section 3.2.3**). The estimated treatment effect and the direction of the effect using each propensity method will be estimated and compared to the primary model.

3.6.4 Bayesian analysis

Lastly, we will estimate the treatment effect in the outcome model using a Bayesian cumulative logistic regression for the primary outcome. This model will calculate the posterior probability distribution for the proportional odds ratio for TAC + APT vs. TAC.

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8.4 Study 2 manuscript

Lother SA, Teng W, Ayilara O, Houston BL, Turgeon AF, Murthy S, Houston DS, Mendelson AA, Farkouh ME, Rush B, Goligher EC, Shaw S, Lawler PR, Keynan Y, Zarychanski R. Therapeutic-dose heparin in combination with antiplatelet agents in non-critically ill patients hospitalized for COVID-19: A secondary analysis of the multiplatform randomized controlled trial (mpRCT). *Pending submission*.

Therapeutic-dose heparin in combination with an antiplatelet agent in non-critically ill patients hospitalized for COVID-19: A secondary analysis of the multiplatform randomized controlled trial (mpRCT)

Authors:

Sylvain A. Lother[1,2], Wen Teng[3], Olawale Ayilara[4], Brett. L. Houston[5,6], Barret Rush[2], Alexis F. Turgeon[7,8], Srinivas Murthy[9], Donald S. Houston[5,6], Asher A. Mendelson[2], Michael E. Farkouh[10], Ewan C. Goligher[11], Souradet Y. Shaw[4], Patrick R. Lawler[12,13], Yoav Keynan*[1,4,14], Ryan Zarychanski*[2,4,5,6]

Affiliations:

1 Section of Infectious Diseases, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
2 Section of Critical Care, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
3 Child Health and Evaluative Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada
4 Department of Community Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
5 Department of Medical Oncology and Hematology, CancerCare Manitoba, Winnipeg, Manitoba, Canada
6 Section of Hematology and Medical Oncology, Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
7 Department of Anesthesiology and Critical Care, Université Laval, Quebec City, Quebec, Canada
8 Population Health and Optimal Health Practices Research Unit, Departments of Traumatology, Emergency Medicine, and Critical Care Medicine, Université Laval Research Center, CHU de Quebec-Université Laval, Quebec City, Quebec, Canada
9 Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada
10 Academic Affairs, Cedars-Sinai Health System, Los Angeles, California, USA
11 Interdepartmental Division of Critical Care Medicine, and the Department of Medicine and Physiology, University of Toronto, Toronto, Onatrio, Canada
12 University of Toronto, Toronto, Ontario, Canada
13 McGill University Health Centre and McGill University, Montreal, Quebec, Canada
14 Department of Medical Microbiology and Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada
*Co-senior authors

Corresponding author: Dr. Sylvain A. Lother
University of Manitoba, Health Sciences Center
GC 436, 820 Sherbrook St, Winnipeg, MB, R3A1R9
+1-(204)-787-2767, Sylvain.Lother@umanitoba.ca
@sylvainlother

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Abstract

Background: Therapeutic-dose heparin improves outcomes in non-critically ill patients with COVID-19. Antiplatelet agents may also lead to improved survival at longer term follow up (180 days). The effect of therapeutic-dose heparin in combination with an antiplatelet agent remains uncertain.

Methods: We conducted a secondary analysis of the multiplatform randomized controlled trial (mpRCT) which enrolled non-critically ill adult patients hospitalized for COVID-19, randomized to receive therapeutic-dose heparin vs. usual care venous thromboembolism prophylaxis. The intervention group included patients who received therapeutic-dose heparin in combination with an antiplatelet agent (ASA or P2Y12 inhibitor) vs. the control group who received therapeutic-dose heparin alone. The primary outcome was an ordinal outcome reflecting survival to hospital discharge without intensive care unit (ICU)-level organ support, survival with organ support, or mortality at day 21. We estimated propensity scores using a logistic regression model and used stabilized inversed probability of treatment weighting for our primary analysis. A proportional odds model was used to estimate the effect of exposure to an antiplatelet agent on the primary outcome.

Results: We included 1,021 patients, 194 received therapeutic-dose heparin in combination with an antiplatelet agent (95.4% ASA) and 827 received therapeutic-dose heparin alone. Patients who received combination treatment were older (67.4 vs. 57.5 years), more likely female (46.4 vs. 38.6%), and more likely to have cardiovascular disease (38.7 vs. 5.7%), diabetes (51.0 vs. 24.9%), and hypertension (76.8 vs. 47.0%). Propensity weighting adequately balanced covariates between intervention and control groups. Exposure to an antiplatelet agent was not associated

with an improvement in survival without the need for ICU-level organ support (76.3 vs. 80.5%, OR 1.07, 95% CI 0.71 – 1.64).

Conclusions: In non-critically ill patients hospitalized for COVID-19 receiving therapeutic-dose heparin, exposure to an antiplatelet agent was not associated with an improvement in survival without the need for organ support.

Introduction

COVID-19 has substantially increased global morbidity and mortality from pneumonia since the onset of the pandemic.[1] Poor clinical outcomes are driven by maladaptive inflammatory and thrombotic host responses to infection, leading to micro- and macro-vascular thrombosis and organ dysfunction.[2-4] In COVID-19 pneumonia, interventions targeted at reducing host inflammatory and thrombotic responses have shown benefit, including anticoagulants and possibly antiplatelet agents.[5,6] Yet the effect of anticoagulants in combination with antiplatelet agents remains uncertain.

In the multiplatform randomized controlled trial (mpRCT), therapeutic-dose anticoagulation with heparin reduces organ dysfunction and improves survival in non-critically ill patients hospitalized for COVID-19 and is now a widely accepted treatment.[5,7,8] ASA, a well-known antiplatelet agent, has demonstrated mixed effects in COVID-19 clinical trials.[9-11] Although ASA demonstrated no improvement in short term mortality (< 30 days)[9,11], there was a suggestion of benefit at longer follow up duration (180 days).[6] Combined anticoagulation and antiplatelet therapy are the cornerstone of therapy for thromboinflammatory conditions such as myocardial infarction,[12] however, the effect of combination therapy on outcomes for infections driving thromboinflammation has not been established.

To investigate whether the combination of therapeutic-dose heparin with an antiplatelet agent is associated with improved survival and reduced need for organ support compared to therapeutic-dose heparin alone, we conducted a propensity weighted analysis of COVID-19 clinical trial data in the mpRCT.

Methods

Study design, setting and population

We conducted a secondary analysis of the mpRCT which included the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) and A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19 (ACTIV-4a) platform trials.[5,13] These multi-center, international, RCTs included non-critically ill patients hospitalized for COVID-19 between April 2020 and January 2021. Patients were randomly assigned to receive therapeutic anticoagulation with either low molecular weight heparin or unfractionated heparin vs. usual care. The ATTACC and ACTIV-4a trial protocols and data were federated and analyzed together, with detailed methods and findings reported in the mpRCT.[5,13] Since therapeutic-dose heparin was shown to improve survival with reduced need for ICU-level organ support, we focused our analysis on patients randomized to receive therapeutic-dose heparin.

Treatment groups

We defined treatment groups as: 1) patients who received therapeutic-dose heparin in combination with an antiplatelet agent (intervention group), and 2) patients who received therapeutic-dose heparin alone (control group). Therapeutic-dose heparin was administered according to local practice algorithms or guidelines for the treatment of venous thromboembolism. Antiplatelet exposure was defined as receiving at least one dose of ASA, or a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) during hospitalization for COVID-19.

Inclusion and exclusion criteria

Patients were included if they were adults aged ≥ 18 years, admitted to hospital with laboratory confirmed SARS-CoV-2 causing COVID-19 disease. Patients were excluded if they received intensive care unit (ICU) level organ support at the time of enrollment. ICU-level organ support was defined as the use of high flow nasal oxygen (HFNO), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), extracorporeal life support (ECLS), vasopressors, and/or inotropes delivered in an ICU or repurposed critical care area. We also excluded patients receiving two or more antiplatelet agents due to bleeding risk.

Outcome measures

The primary outcome was a 3-level ordinal outcome reflecting survival to hospital discharge without ICU-level organ support, survival to hospital discharge with ICU-level organ support, or mortality in the first 21 days following randomization. Secondary outcomes included survival without ICU-level respiratory support (including HFNO, NIV, IMV), survival without need for IMV, 90-day mortality, hospital free days to day 28, and total thrombotic events (any systemic arterial embolization, stroke, or MI, DVT or PE) (**Appendix 1**). Safety outcomes included major bleeding as defined by the International Society on Thrombosis and Haemostasis,[14] and transfusion of ≥ 2 red blood cell units.

Appendix 1: Description of primary and secondary outcome measures

#	Endpoint	Variable type	Description
1.0	Survival without ICU-level organ support	Ordinal	3 level ordinal outcome based on the worst status of each patient through day 21 a) Survival without ICU-level organ support b) Survival with ICU-level organ support c) Death
2.1	Survival without ICU-level respiratory support	Ordinal	3 level ordinal outcome based on the worst status of each patient through day 21 a) Survival without HFNO, NIMV or IVM (without respiratory support) b) Survival with HFNO, NIV or IMV

			c) Death
2.2	Survival without need for IMV	Dichotomous	2 level outcome based on worst status of each patient through day 21 a) Survival without IMV b) IMV and/or death
2.3	90-day mortality	Dichotomous	2 level outcome measured at day 90 a) Survival b) Death
2.4	Hospital free days	Ordinal	Number of days not admitted to hospital within the first 21 days (range -1 to 21, where -1 indicates death)
2.5	Total thrombotic events	Dichotomous	2 level outcome measured at day 21 a) Thrombotic event (MI, stroke, arterial embolization, DVT, PE) b) No thrombotic event
2.6	Major bleeding	Dichotomous	2 level outcome measured at day 14 a) Major bleeding event b) No major bleeding event
2.7	Transfusion ≥ 2 units pRBC	Dichotomous	2 level outcome measured at day 14 a) Received ≥ 2 units pRBC b) Did not receive ≥ 2 units pRBC

DVT = deep venous thrombosis; HFNO = high flow nasal oxygen; ICU = intensive care unit; IMV = invasive mechanical ventilation; MI = myocardial infarction; NIV = non-invasive ventilation; PE = pulmonary embolism; pRBC = packed red blood cells

Baseline comparisons of treatment groups

We summarized baseline characteristics as means with standard deviations (for continuous variables) and proportions (for categorical variables). Standardized mean differences were used to compare baseline characteristics between the intervention and control groups.[15]

Propensity score estimation

Propensity scores were used to estimate a patient's probability of receiving an antiplatelet agent given their baseline characteristics. We estimated the propensity score using a logistic regression model where the exposure to an antiplatelet agent was regressed on 19 covariates (**Appendix 2**). Covariates were selected using input from content experts to control for patient characteristics that could affect the primary outcome (possible confounder) or both the administration of an antiplatelet agent and the primary outcome (confounder). Age, platelet count, and creatinine were modeled as continuous variables, d-dimer was categorized as high (≥2x upper limit of

normal [ULN]) or low (< 2x ULN) according to local laboratory criteria, baseline respiratory support was categorized as no requirements for oxygen, receipt of low-flow oxygen, or high-flow oxygen. Comorbid conditions were dichotomized as present or absent. Cardiovascular disease was defined as having at least one of the following baseline conditions: heart failure, coronary artery disease, peripheral arterial disease, or cerebrovascular disease (stroke or transient ischemic attack). Missing data for continuous variables was handled by imputing the median for missing data points, and by imputing '0 = absent' for dichotomous comorbidity variables.

Appendix 2: Logistic regression describing the influence of covariates on exposure to an antiplatelet agent in patients randomized to receive therapeutic anticoagulation with heparin in the mpRCT

Covariate	Description	Odds ratio	95% CI
Age	Continuous variable	0.01	0.001 – 0.05**
Sex	Male	Ref	
	Female	1.14	0.75 – 1.73
Race	White	Ref	
	Asian	0.95	0.27 – 3.32
	Black	1.38	0.82 – 2.33
	First Nations	0.31	0.06 – 1.59
	Other	0.90	0.19 – 4.31
	Unknown	2.28	1.03 – 5.04**
Ethnicity	Not Hispanic/Latino	Ref	
	Hispanic/Latino	0.68	0.33 – 1.39
	Unknown	0.44	0.12 – 1.70
BMI	< 18.5	Ref	
	18.5 – 24.9	0.33	0.07 – 1.59
	25 – 29.9	0.63	0.14 – 2.91
	30 – 34.9	0.88	0.19 – 4.14
	35 – 39.9	0.68	0.14 – 3.42
	> 40	0.81	0.16 – 4.00
	Unknown	0.37	0.07 – 1.86
Immunosuppression	Absent	Ref	
	Present	1.53	0.82 – 2.87
Cardiovascular disease	Absent	Ref	
	Present	6.11	3.74 – 9.98**
Respiratory disease	Absent	Ref	
	Present	1.09	0.68 – 1.75
Diabetes	Absent	Ref	
	Present	2.09	1.38 – 3.17**
Hypertension	Absent	Ref	
	Present	1.32	0.83 – 2.09
CKD	Absent	Ref	

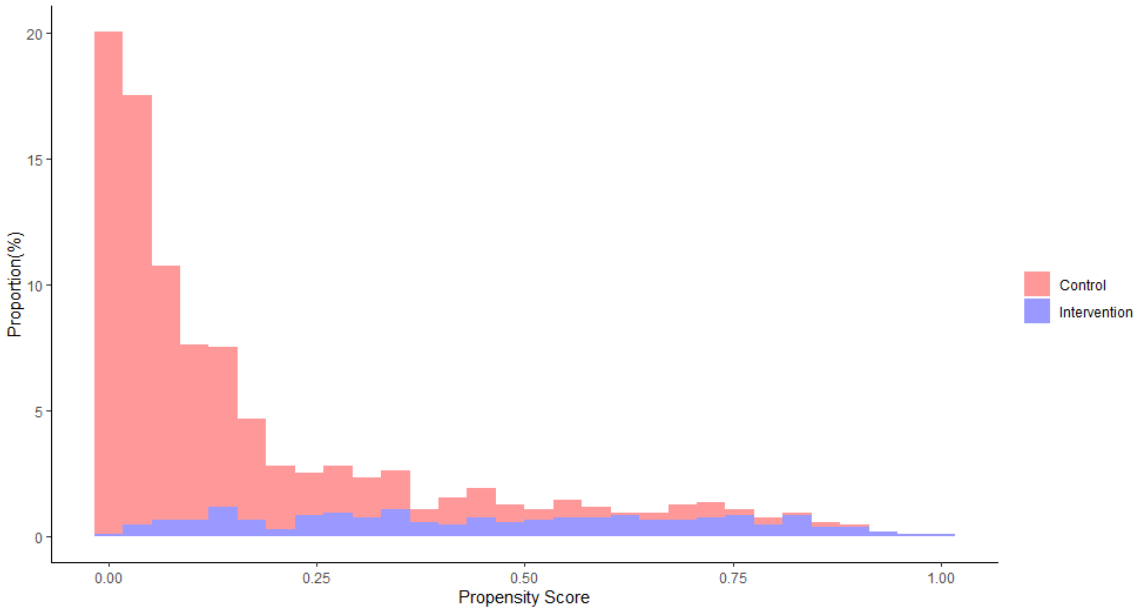
	Present	1.42	0.73 – 2.77
Liver disease	Absent	Ref	
	Present	0.99	0.23 – 4.20
Respiratory support	No O2	Ref	
	Low-flow O2	1.00	0.53 – 1.88
	High-flow O2	0.72	0.15 – 3.43
	Unspecified	1.13	0.46 – 2.80
Creatinine	Continuous variable	1.06	0.90 – 1.24
Platelet count	Continuous variable	1.00	1.00 – 1.00
D-dimer	Low	Ref	
	High	1.54	0.98 – 2.41
	Unknown	1.10	0.61 – 1.97
Corticosteroid treatment	No	Ref	
	Yes	1.88	1.18 – 2.97**
Remdesivir treatment	No	Ref	
	Yes	2.18	0.16 – 29.06
Country of enrolment	Canada	Ref	
	Brazil	0.42	0.14 – 1.26
	USA	0.97	0.47 – 1.97

**Statistically significant; BMI = body mass index; CI = confidence interval

Methods to achieve balance between treatment groups

We conducted a feasibility assessment to evaluate the overlap of propensity score distributions between the intervention and control groups (**Appendix 3**). To adjust for imbalances, we converted propensity scores to stabilized inverse probability of treatment weights (IPTW). The ability of the propensity model to balance covariates across the intervention and control groups was evaluated using mean standardized differences (**Table 1**). An absolute standardized difference < 0.1 was considered adequate for covariate balance.[16] The stabilized IPTW model was chosen *a priori*, prior to estimating the treatment effect.

Appendix 3: Histogram distribution of propensity scores between intervention group and control group



176

177 *Stabilized inverse probability of treatment weighting*

178 Weights were calculated from propensity scores to create a pseudo-population where the
179 distribution of confounding variables were balanced between the intervention and control groups.
180 Each patient was assigned a weight equal to the inverse of their propensity score. Since inverse
181 weighting of extreme propensity scores (scores approaching 0 in the intervention group; or
182 scores approaching 1 in the control group) can lead to disproportionate influence from patients
183 with extreme scores, we adjusted individual weights with *stabilized* IPTW, standardized to the
184 overall mean of the propensity score.[17] The propensity model was also evaluated for
185 misspecification by calculating the mean and range of *stabilized* IPTW.

186

187 *Statistical analyses*

188 Population characteristics were summarized for continuous variables as means (standard
189 deviation) and categorical variables as percentages. Between group differences were analyzed by
190 Chi-square and t-tests for categorical and continuous data, respectively. We used a proportional

odds model to estimate the effect of exposure to an antiplatelet agent on the primary outcome. Effect comparisons were presented as odds ratios (OR), where an OR > 1 for the primary outcome represents greater odds of survival to hospital discharge without ICU-level organ support. Effect estimates for secondary outcomes were calculated using binary logistic regression for dichotomous outcomes, and proportional odds model for ordinal outcomes. Sensitivity analyses were conducted (planned *a priori*) by adding covariates which remained unbalanced after weighting (SD > 0.1) to the proportional odds model to control for any potential residual confounding. All analyses were conducted using R version 4.2.2 using the twang package.[18]

Results

Baseline characteristics

We included 1,021 patients from the mpRCT who were randomized to receive therapeutic-dose heparin (**Figure 1**). The overall rate of concurrent antiplatelet agent exposure was 19% (n=194). The most used antiplatelet was aspirin (n=186; 95.4%). At baseline, patients who received therapeutic-dose heparin in combination with an antiplatelet agent were older (67.4 vs. 57.5 years), more likely female (46.4 vs. 38.6%), and more likely to have comorbidities such as cardiovascular disease (38.7 vs. 5.7%), diabetes (51.0 vs. 24.9%), and hypertension (76.8 vs. 47.0%), compared with those who received therapeutic-dose heparin alone. Baseline covariates before and after weighting are reported in **Table 1**.

Table 1: Baseline characteristics of patients exposed and unexposed to an antiplatelet agent in patients randomized to receive therapeutic-dose heparin in the mpRCT before and after stabilized inverse probability of treatment weighting

	Unweighted cohort			**Weighted cohort post stabilized IPTW**			
Variable	TAC + APT (n=194)	TAC alone (n=827)	SD	TAC + APT (n=60)[&]	TAC alone (n=652)[&]	SD	%Δ SD
Age (years), mean (SD)	67.4 (11.6)	57.5 (14.0)	0.702*	62.0 (13.9)	59.7 (14.5)	0.163*	77
Female sex (%)	46.4	38.6	0.160*	37.8	39.1	-0.027	83

Race (%)							
White	52.1	54.7	-0.052	58.1	54.2	0.076	0
Asian	2.6	3.9	-0.069	1.2	3.3	-0.114*	0
Black	30.9	16.2	0.375*	18.8	18.7	0.001	100
Indigenous	1.5	12.2	-0.353*	1.6	1.0	-0.284*	20
Ethnicity (%)							
Hispanic or Latino	21.6	48.9	-0.548*	41.2	44.5	-0.067	88
BMI, mean (SD)	32.3 (7.8)	31.1 (7.7)	0.151*	31.8 (7.4)	31.2 (7.8)	0.081	46
Comorbidities (%)							
Immunosuppression	14.9	6.7	0.302*	7.9	8.2	-0.011	96
CVD	38.7	5.7	1.017*	15.3	13.3	0.061	94
Respiratory disease	27.3	15.7	0.302*	32.3	18.4	0.364*	0
Diabetes	51.0	24.9	0.571*	32.3	30.2	0.045	92
Hypertension	76.8	47.0	0.596*	52.9	53.1	-0.003	99
CKD	20.1	4.5	0.595*	9.0	8.9	0.004	99
Oxygen support (%)							
No oxygen	12.9	15.4	-0.069	23.6	15.3	0.233*	0
Low flow oxygen	74.2	76.7	-0.057	67.9	76.2	-0.195*	0
High flow oxygen	2.6	1.3	0.100*	1.1	1.4	-0.029	71
Co-treatments (%)							
Corticosteroids	10.3	5.0	0.226*	9.1	5.2	0.165*	27
Remdesivir	0.5	0.2	0.051	0.2	0.2	-0.006	88
Lab values mean (SD)							
Creatinine (mg/dL)	1.4 (1.9)	1.0 (0.8)	0.341*	1.2 (1.3)	1.1 (1.0)	0.027	92
Platelets (x 10^9)	216 (80)	243 (103)	-0.272*	224 (81)	236 (102)	-0.124*	54
D-dimer (ULN)[#]	4.1 (8.5)	2.6 (4.3)	0.276*	2.7 (5.1)	2.7 (4.2)	-0.005	98
Country (%)							
Brazil	8.8	26.2	-0.416*	22.3	23.0	-0.017	96
Canada	11.9	9.2	0.090	7.6	9.4	-0.061	32
United States	77.3	47.3	0.602*	67.0	53.4	0.273*	55

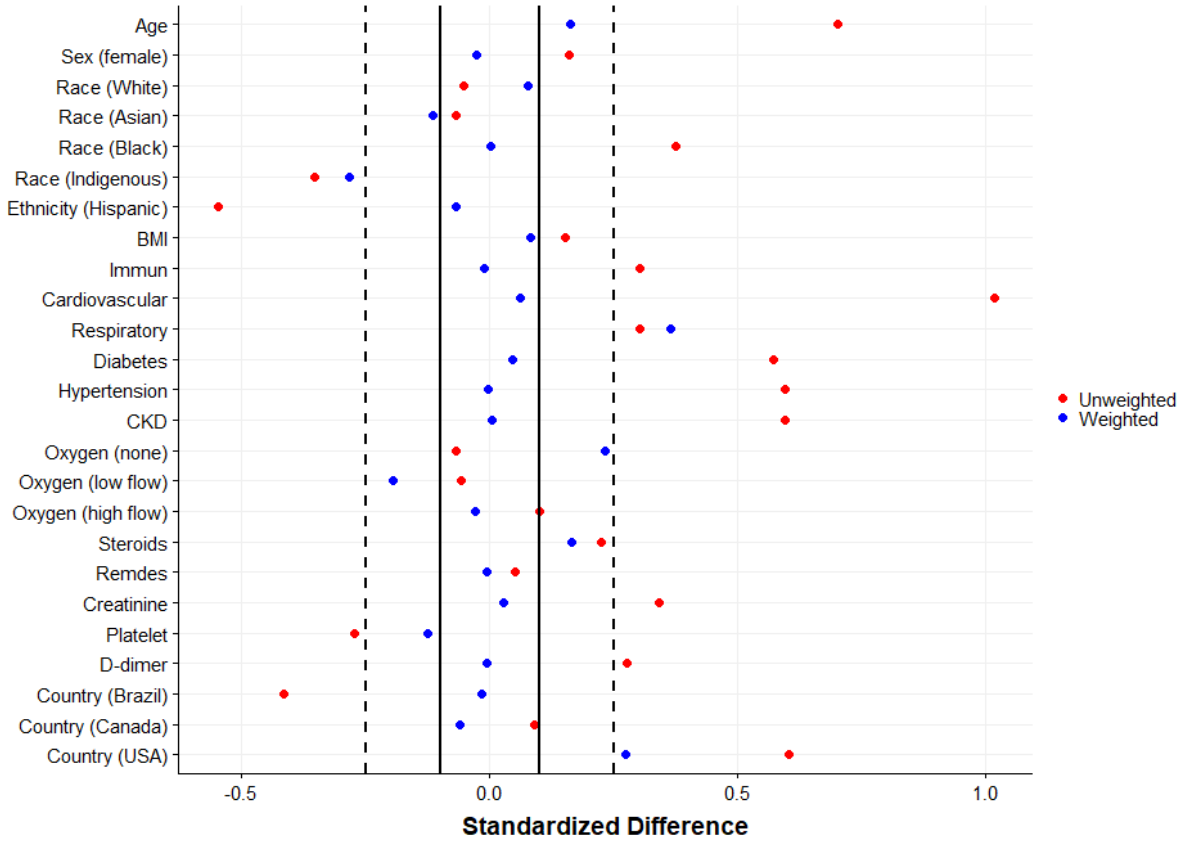
*Absolute SD > 0.1; & effective sample size after weighting; # d-dimer was measured as the a ratio above the ULN according to local laboratory criteria; %Δ SD = absolute percentage reduction in standardized difference; APT = antiplatelet; BMI = body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease; IPTW = inverse probability of treatment weighting; SD = standardized difference; TAC = therapeutic-dose anticoagulation; Var ratio = variance ratio

Comparison of baseline covariate distribution before and after propensity weighting

Covariates that were found to significantly influence exposure to an antiplatelet agent included age, baseline history of cardiovascular disease or diabetes, and receipt of corticosteroids (**Appendix 2**). Absolute standardized differences exceeded 0.1 in 76% of variables at baseline. After propensity weighting, covariate balance was improved between groups with standardized differences > 0.1 in 36% of covariates (**Table 1**). In the weighted cohort, absolute standardized differences ranged from 0.001 to 0.364, with a median of 0.061 (IQR 0.017 – 0.134) (**Appendix**

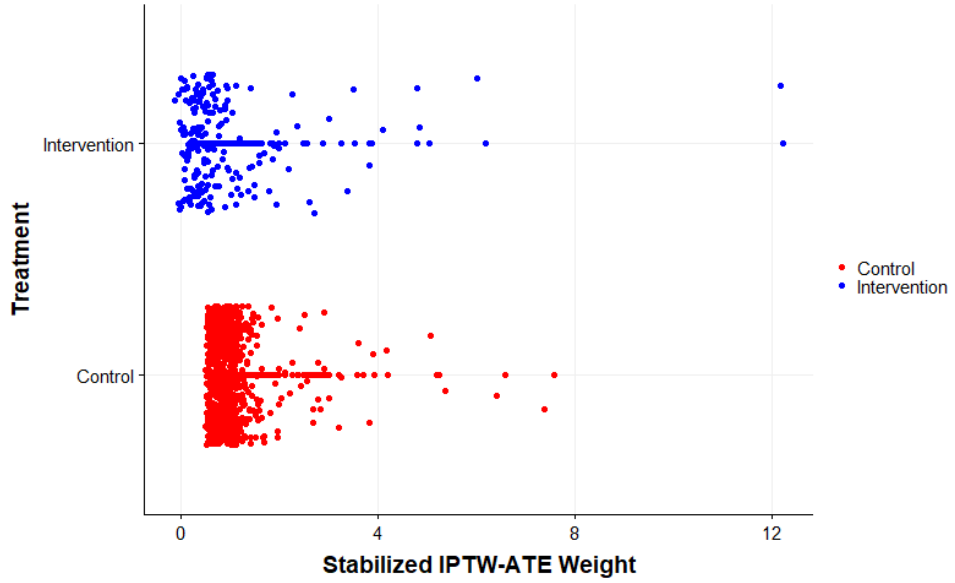
4). The mean stabilized IPTW was 0.816 (SD 1.220, range 0.190 – 12.220) in the intervention group and 1.009 (SD 0.523, range 0.810 – 7.580) in the control group (**Appendix 5**).

Appendix 4: Covariate balance measured by standardized difference in the unweighted and weighted cohorts



BMI = body mass index; CKD = chronic kidney disease; Immun = immunocompromised; Remdes = remdesivir

Appendix 5: Cloud-plot of the distribution of stabilized IPTW between the intervention and control groups



Estimation of treatment effects

Exposure to an antiplatelet agent was not associated with an improvement in survival without ICU-level organ support in patients receiving therapeutic-dose heparin (OR 1.07, 95% CI 0.71 – 1.64, p = 0.764). Of the patients in the intervention group 76.3% survived to hospital discharge without ICU-level organ support compared with 80.5% in the control group.

Secondary outcomes

Exposure to an antiplatelet agent was not associated with significant changes in major bleeding, the requirement for transfusion of ≥ 2 red blood cell units, or any other secondary outcome (**Table 2**). Patients receiving therapeutic-dose heparin in combination with an antiplatelet agent had a numeric increase in the number of major bleeding events compared with those receiving therapeutic-dose heparin alone, although overall events were low (4.1 vs. 1.0%, OR 1.69, 95% CI 0.43 – 5.19).

Table 2: The effect of exposure to an antiplatelet agent on secondary outcomes in patients receiving therapeutic-dose heparin

Secondary outcome	TAC + APT	TAC alone	OR	95% CI	p-value
Survival to hospital discharge without ICU-level RS support (%)	83.1	84.8	1.58	0.93 – 2.68	0.088
Survival to hospital discharge without need for IMV (%)	75.3	80.0	0.35	0.06 – 1.13	0.138
90-day mortality (%)	11.9	8.8	0.65	0.33 – 1.19	0.191
Hospital free days (days)	20.3	21.2	1.03	0.77 – 1.38	0.857
Total thrombosis (%)	3.1	1.7	0.55	0.09 – 1.95	0.434
Major bleeding events (%)	4.1	1.0	1.69	0.43 – 5.19	0.393
Transfusion of ≥ 2 RBC units (%)	2.1	0.4	3.67	0.59 – 19.13	0.121

APT = antiplatelet; CI = confidence interval; ICU = intensive care unit; IMV = invasive mechanical ventilation; OR = odds ratio; RBC = red blood cell; RS = respiratory; TAC = therapeutic anticoagulation

Sensitivity analysis

We conducted sensitivity analyses for the primary outcome by adding unbalanced covariates (SD > 0.1) after propensity weighting that were felt to potentially clinically influence the outcome, into the proportional odds model (**Appendix 5**). All sensitivity analyses yielded similar treatment effects, with no significant differences observed in the primary outcome.

Appendix 5: Effect estimates for the primary outcome (survival to hospital discharge without ICU-level organ support) using different propensity analytic methods and by adding covariates that remained imbalanced (SD > 0.1) into the models to adjust for potential residual confounding

Sensitivity analysis model	OR	95% CI
Primary model: Treatment exposure only	1.07	0.71 – 1.64
Sensitivity analysis: Treatment exposure and age covariates in the model	1.12	0.74 – 1.72
Sensitivity analysis: Treatment exposure, age, respiratory disease, and receipt of corticosteroids in the model	1.12	0.74 – 1.73

APT = antiplatelet; CI = confidence interval; IPTW = inverse probability of treatment weighting; OR = odds ratio; TAC = therapeutic anticoagulation

Discussion

In non-critically ill patients hospitalized for COVID-19 that were included in the mpRCT and randomized to receive therapeutic-dose heparin, the exposure to an antiplatelet agent did not

significantly improve survival to hospital discharge without ICU-level organ support, compared to treatment with therapeutic-dose heparin alone. There was a trend towards worse outcomes in the group exposed to an antiplatelet agent, with a reduced proportion of patients surviving without ICU-level organ support (absolute risk increase 4%). While major bleeding events were numerically higher in the treatment group, total events were low and predominantly driven by the need for blood transfusion.

The findings are consistent with limited clinical trial evidence showing no benefit to combination treatment in COVID-19. The Bayesian adaptive ACTIV-4a trial (n=562) randomized patients to receive therapeutic-dose heparin plus a P2Y12 inhibitor vs. therapeutic-dose heparin alone. The antiplatelet exposure was predominantly with ticagrelor (63%) or clopidogrel (37%) for up to 14 days. Combination treatment did not improve the number of organ support-free days (aOR 0.83, 95% credible interval (CrI) 0.55-1.25, posterior probability of inferiority 81%). Major bleeding occurred in 6 vs. 2 patients in the treatment and control groups, respectively.[19] Our study adds to the overall evidence that combination treatment with ASA is similarly ineffective to combination with a P2Y12 inhibitors. In contrast, a retrospective observational study of admitted patients with COVID-19 revealed reduced in-hospital mortality in patients who received combination treatment (aHR 0.11, 95% CI 0.03-0.45) and patients who received therapeutic-dose anticoagulation alone (aHR 0.13, 95% 0.03-0.53) compared to prophylactic-dose anticoagulation alone. This study was limited by its design, representative of a single center and small sample size (n=242).[20]

Therapeutic-dose heparin alone has consistently been shown to improve outcomes in RCTs of non-critically ill patients with COVID-19.[5,21-24] In the large mpRCT (n=2,219), therapeutic-dose heparin reduced the composite ordinal endpoint of progression to ICU-level organ support and death compared with usual care (aOR 1.27, 95% CrI 1.03-1.58, posterior probability for superiority 98.6%).[5] In contrast, antiplatelet agents alone have shown mixed results in 4 RCTs of hospitalized COVID-19 patients.[9,11,19,25] The RECOVERY trial (n=14,892) demonstrated no effect on 28-day mortality and no difference in the composite outcome of ventilation or death, but there was a significant yet small reduction in thrombotic events (4.6 vs. 5.3%, absolute difference -0.6%, standard error 0.4%).[11] The ACTIV-4a (n=1,549) and COVID-PACT (n=292) trials did not demonstrate benefit with ASA or P2Y12 inhibitors alone.[9,25] In the REMAP-CAP Bayesian adaptive platform trial (n=1,546) which included only critically ill patients, randomization to an antiplatelet agent was associated with a 95% probability of improved 6-month survival.[6] The practical implications of these findings have led to recommendations to use therapeutic-dose heparin alone, while the role of antiplatelet agents alone and in combination with therapeutic-dose heparin are not recommended.[7,8]

Strengths of this study included the use of a robust clinical trial dataset with prospectively collected data which reliably captured patient baseline factors, COVID-19 illness severity, treatment factors and outcomes. We used a comprehensive propensity weighting analysis which reduced potential confounding and appropriately balanced covariates, including baseline cardiovascular disease and diabetes which were significantly associated with the exposure to an antiplatelet agent. While some covariates remained unbalanced after weighting, we conducted

comprehensive sensitivity analyses to account for potential residual confounding which yielded similar effect estimates, increasing confidence in the results.

The major limitation of our study was our inability to balance and control for all covariates (known or unknown) that might influence whether a patient receives an antiplatelet agent. Remaining between group differences in covariate balance was most common in covariates that had a low prevalence, and thus unlikely to significantly impact the results. Additionally, we utilized a clinical trial population which included a selected patient population which doesn't reflect real world practice. This population was enrolled early in the pandemic, prior to widespread adoption of known beneficial therapies for COVID-19. Since our analysis showed no benefit, this is unlikely to change the relevance of our findings. Lastly, the trial data set was limited to shorter-term outcomes (up to 90 days), limiting our ability to test the hypothesis that the addition of antiplatelet agents could be beneficial at longer-term follow up (such as 180 days).

The duration of exposure to an antiplatelet agent and proportion of patients on antiplatelets prior to COVID-19 illness was not recorded in our dataset, thus the effect of exposure duration and indication for antiplatelet use is unknown. It's possible that duration of exposure and follow up duration was too short to observe a treatment effect in COVID-19. Additionally, our analysis was limited to patients with COVID-19 pneumonia, and little is known of the effects of therapeutic-dose heparin, antiplatelet agents, and their use in combination in other etiologies of pneumonia. Overall, the combination of therapeutic-dose heparin and antiplatelet agents is likely safe, with

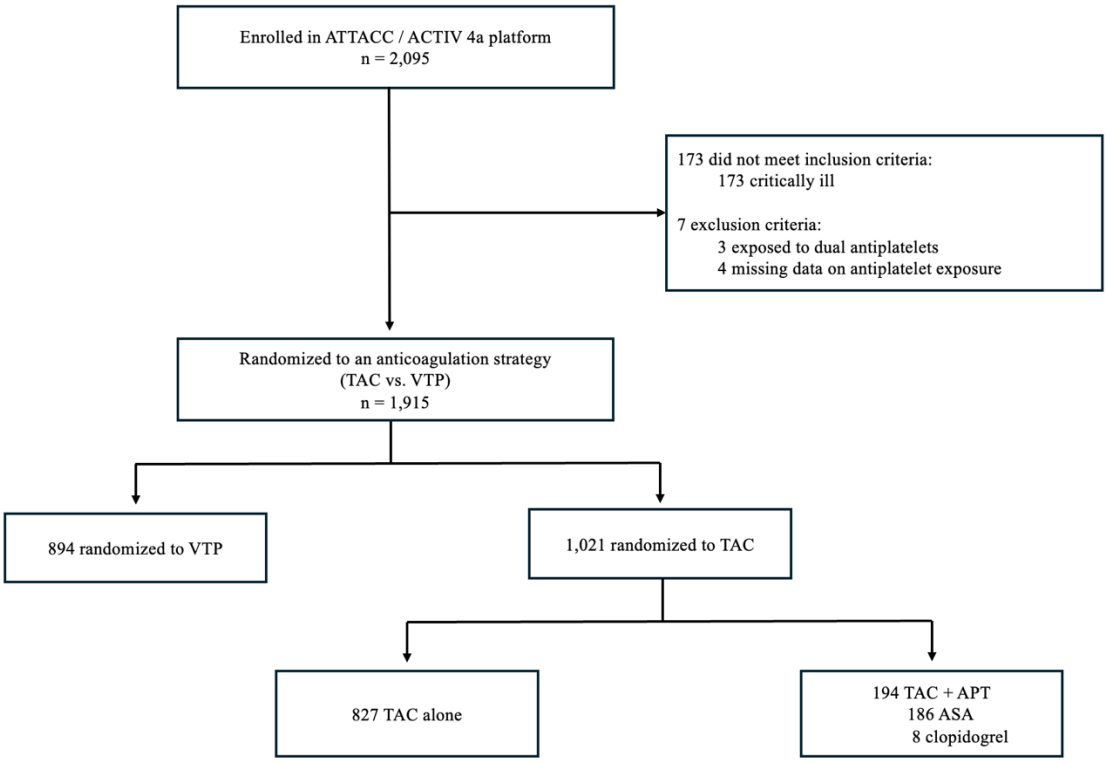
low frequency of major bleeding events. Further well-designed RCTs that evaluate the effect of anticoagulants, antiplatelet agents, and their interactions in acute infections are needed.

Conclusion

In non-critically ill patients hospitalized for COVID-19 receiving therapeutic-dose heparin, exposure to an antiplatelet agent was not associated with an improvement in survival without ICU-level organ support.

Tables and Figures

Figure 1: Study flow sheet



APT = antiplatelet agent; TAC = therapeutic-dose anti-coagulation; VTP = venous thromboprophylaxis

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8.5 Supplementary propensity analyses

Supplementary analyses for the following manuscript:

Lother SA, Teng W, Ayilara O, Houston BL, Turgeon AF, Murthy S, Houston DS, Mendelson AA, Farkouh ME, Rush B, Goligher EC, Shaw S, Lawler PR, Keynan Y, Zarychanski R. Therapeutic-dose heparin in combination with antiplatelet agents in non-critically ill patients hospitalized for COVID-19: A secondary analysis of the multiplatform randomized controlled trial (mpRCT)

We planned several sensitivity analyses to evaluate the treatment effect after controlling for possible residual confounding. First, we reanalyzed the treatment effect using stabilized inverse probability of treatment weights (IPTW) after adding clinically important covariates that remained unbalanced (standardized difference [SD] > 0.1) after propensity weighting into the proportional odds model. Second, we re-estimated stabilized IPTW after accounting for possible non-linear relationships between unbalanced continuous variables and the probability of receiving an antiplatelet. Lastly, we re-estimated propensity matching. The effect estimates for all sensitivity analyses are summarized in **Table S1**. Further details are provided in the remainder of this appendix.

Table S1: Effect estimates for the primary outcome (survival to hospital discharge without ICU-level organ support) using sensitivity analyses

Sensitivity analysis model	OR	95% CI
Primary model: **Stabilized IPTW** With treatment exposure only	1.07	0.71 – 1.64
Sensitivity analysis 1: **Stabilized IPTW** With treatment exposure and age covariates in the model	1.12	0.74 – 1.72
Sensitivity analysis 2: **Stabilized IPTW** With treatment exposure, age, respiratory disease, and receipt of corticosteroids in the model	1.12	0.74 – 1.73
Sensitivity analysis 3: **Stabilized IPTW** With non-linear effect of age with treatment exposure only	1.09	0.73 – 1.67
Sensitivity analysis 4: **Stabilized IPTW**	1.08	0.72 – 1.67

With non-linear effect of age with treatment exposure and respiratory disease		
Sensitivity analysis 5: **Propensity matching** With treatment exposure only	0.98	0.56 – 1.69

APT = antiplatelet; CI = confidence interval; IPTW = inverse probability of treatment weighting; OR = odds ratio; TAC = therapeutic anticoagulation

Sensitivity analysis 1: Re-estimating the treatment effect by adding age into the outcome model

We generated propensity scores using a logistic regression model where the exposure to an antiplatelet agent was regressed on 19 covariates. Propensity scores were converted to stabilized IPTW. We used a proportional odds model to estimate the effect of exposure to an antiplatelet agent on the primary outcome. Given age remained unbalanced after stabilized IPTW (SD 0.163) and was deemed to be a clinically important residual confounder, we added age along with the treatment exposure into the outcome model. When controlling for age, exposure to an antiplatelet was not associated with an improvement in survival without ICU-level organ support (OR 1.12, 95% CI 0.74 – 1.72) (**Table S1**).

Sensitivity analysis 2: Re-estimating the treatment effect by adding age, respiratory disease, and receipt of corticosteroids in the outcome model

The same approach was used to generate stabilized IPTW as in the primary analysis. Additional variables remained unbalanced after stabilized IPTW that were deemed to potentially influence the estimation of the treatment effect, including age (SD 0.163), respiratory disease (SD 0.364), and receipt of corticosteroids (SD 0.165). We added these variables into the outcome model along with the treatment exposure. When controlling for age, respiratory disease, and receipt of corticosteroids, exposure to an antiplatelet was not associated with an improvement in survival without ICU-level organ support (OR 1.12, 95% CI 0.74 – 1.73) (**Table S1**).

Sensitivity analysis 3: Re-calculating stabilized IPTW controlling for non-linear effects of age

Given the residual imbalance in age between treatment groups after stabilized IPTW in the primary model (SD 0.163), we considered that age potentially had a non-linear relationship with

exposure to an antiplatelet agent. When controlling for the non-linear relationship between age and the exposure, the resulting stabilized IPTW resulted in improved balance in age between treatment groups (SD 0.042) (**Table S2**). Balance in the remaining variables were similar to the primary model. Using this modified pseudo-population, we estimated the treatment effect using the primary outcome model. Exposure to an antiplatelet was not associated with an improvement in survival without ICU-level organ support (OR 1.09, 95% CI 0.73 – 1.67) (**Table S1**).

Table S2: Baseline characteristics of patients exposed and unexposed to an antiplatelet agent in patients randomized to receive therapeutic-dose heparin in the mpRCT, before and after stabilized IPTW, and adjusting for the non-linear effects of age

	Unweighted cohort			**Weighted cohort post stabilized IPTW**			
Variable	TAC + APT (n=194)	TAC alone (n=827)	SD	TAC + APT (n=48.7)	TAC alone (n=659.4)	SD	%Δ SD
Age (years) mean (SD)	67.4 (11.6)	57.5 (14.0)	0.702*	60.2 (15.9)	59.6 (14.3)	**0.042**	94
Female sex (%)	46.4	38.6	0.160*	35.4	39.1	-0.076	53
Race (%)							
White	52.1	54.7	-0.052	54.9	54.3	0.011	79
Asian	2.6	3.9	-0.069	1.2	3.4	-0.118*	0
Black	30.9	16.2	0.375*	17.8	18.5	-0.019	95
Indigenous	1.5	12.2	-0.353*	1.6	1.0	-0.286*	19
Ethnicity (%)							
Hispanic or Latino	21.6	48.9	-0.548*	39.1	44.6	-0.112*	80
BMI mean (SD)	32.3 (7.8)	31.1 (7.7)	0.151*	32.4 (7.5)	31.2 (7.8)	0.148*	2
Comorbidities (%)							
Immunosuppression	14.9	6.7	0.302*	7.4	8.1	-0.027	91
CVD	38.7	5.7	1.017*	14.8	13.2	0.051	95
Respiratory disease	27.3	15.7	0.302*	34.6	18.2	0.428*	0
Diabetes	51.0	24.9	0.571*	30.4	30.3	0.003	93
Hypertension	76.8	47.0	0.596*	50.8	52.9	-0.042	93
CKD	20.1	4.5	0.595*	8.4	8.8	-0.012	98
Oxygen support (%)							
No oxygen	12.9	15.4	-0.069	22.2	15.3	0.196*	0
Low flow oxygen	74.2	76.7	-0.057	69.9	76.2	-0.147*	0
High flow oxygen	2.6	1.3	0.100*	1.0	1.4	-0.030	70
Co-treatments (%)							
Corticosteroids	10.3	5.0	0.226*	8.6	5.3	0.143*	37
Remdesivir	0.5	0.2	0.051	0.2	0.3	-0.008	84
Lab values mean (SD)							
Creatinine (mg/dL)	1.4 (1.9)	1.0 (0.8)	0.341*	1.1 (1.3)	1.1 (1.0)	0.014	96
Platelets (x 10^9)	216 (80)	243 (103)	-0.272*	220 (81)	236 (102)	-0.168*	38
D-dimer (mg/L)	4.1 (8.5)	2.6 (4.3)	0.276*	2.6 (5.1)	2.7 (4.2)	-0.018	94
Country (%)							
Brazil	8.8	26.2	-0.416*	20.9	23.0	-0.049	88
Canada	11.9	9.2	0.090	7.3	9.4	-0.072	20
United States	77.3	47.3	0.602*	68.9	53.4	0.310*	49

Sensitivity analysis 4: Re-estimating the treatment effect by using the pseudo-population adjusting for non-linear effects of age and adding respiratory disease in the outcome model

The same pseudo-population included in sensitivity analysis 3 was used, adjusting for the non-linear effects of age. Given residual imbalance in baseline respiratory disease, we added this covariate to the outcome model. When controlling for respiratory disease, exposure to an antiplatelet was not associated with an improvement in survival without ICU-level organ support (OR 1.08, 95% CI 0.72 – 1.67) (**Table S1**).

Sensitivity analysis 5: Propensity matching

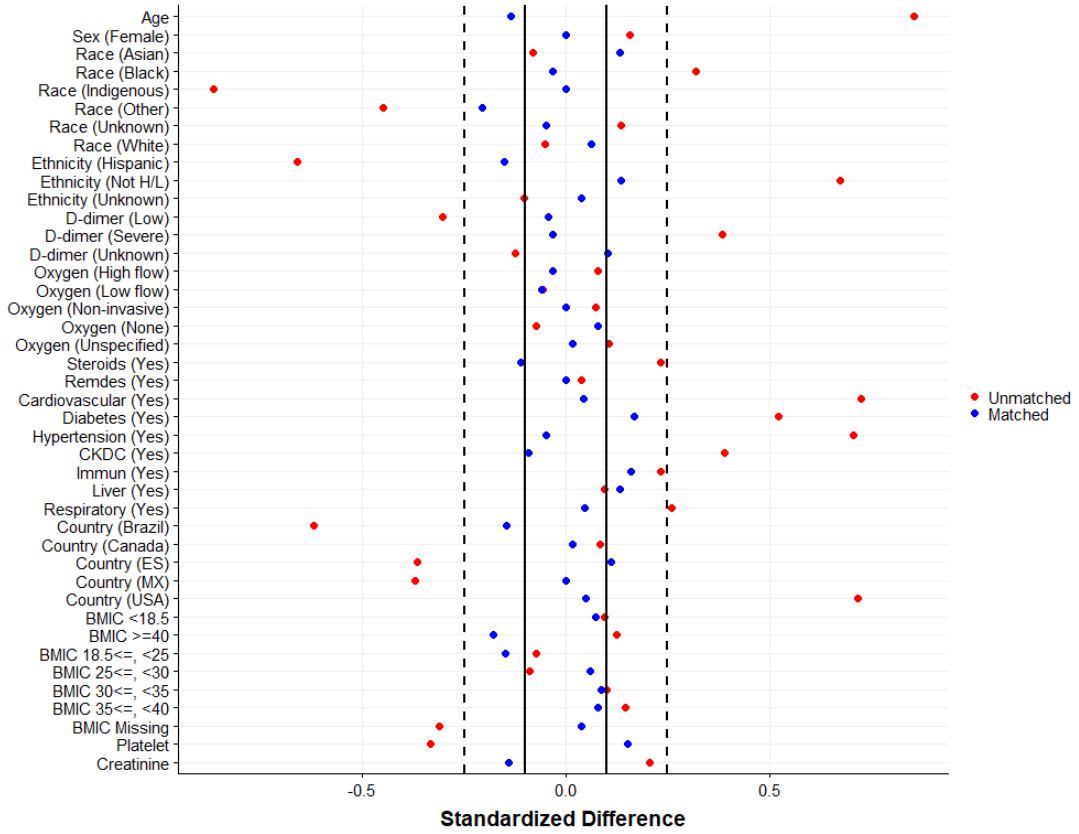
To compare the influence of different propensity analytic methods in covariate balance and estimation of the treatment effect, we performed a propensity matched analysis using 1:1 nearest neighbour matching with replacement. Propensity matching resulted in adequate balance in covariates between treatment groups (**Table S3, Figure S1**). Exposure to an antiplatelet was not associated with an improvement in survival without ICU-level organ support (OR 0.98, 95% CI 0.56 – 1.69) (**Table S1**).

Table S3: Baseline characteristics of patients exposed and unexposed to an antiplatelet agent in patients randomized to receive therapeutic-dose heparin in the mpRCT, before and after propensity matching

	Unmatched cohort			**Matched cohort**				
Variable	TAC + APT (n=194)	TAC alone (n=827)	SD	TAC + APT (n=192)	TAC alone (n=113)	SD	%Δ SD	Var ratio
Age (years) mean	67.4	57.5	0.855*	67.2	68.8	-0.135*	84	0.69
Female sex (%)	46.4	38.6	0.157*	46.4	46.4	0	100	
Race (%)								
White	52.1	54.7	-0.052	52.1	49.0	0.063	0	
Asian	2.6	3.9	-0.082	2.6	0.5	0.131*	0	
Black	30.9	16.2	0.319*	30.7	32.3	-0.034	89	
Indigenous	1.5	12.2	-0.864*	1.5	1.5	0	100	
Ethnicity (%)								
Hispanic or Latino	21.6	48.9	-0.660*	21.9	28.1	-0.152*	77	
Comorbidities (%)								
Immunosuppression	14.9	6.7	0.233*	15.1	9.4	0.161*	31	
CVD	42.3	6.5	0.723*	41.7	39.6	0.042	94	
Respiratory disease	27.3	15.7	0.260*	27.6	25.5	0.047	82	
Diabetes	51.0	24.9	0.523*	51.0	42.7	0.167*	68	
Hypertension	76.8	47.0	0.705*	77.1	79.2	-0.049	93	
CKD	20.1	4.5	0.390*	19.8	23.4	-0.091	77	

Oxygen support (%)								
No oxygen	12.9	15.4	-0.074	13.0	10.4	0.078	0	
Low flow oxygen	74.2	76.7	-0.056	74.5	77.1	-0.060	0	
High flow oxygen	2.6	1.3	0.079	2.6	3.1	-0.033	58	
Co-treatments (%)								
Remdesivir	0.5	0.2	0.038	0.5	0.5	0	100	
Lab values mean								
Creatinine (mg/dL)	1.4	1.0	0.207*	1.4	1.7	-0.141*	32	1.03
Platelets (x 10^9)	216	243	-0.332*	216	204	0.151*	55	1.04
Country (%)								
Brazil	8.8	26.2	-0.618*	8.9	13.0	-0.147*	76	
Canada	11.9	9.2	0.082	12.0	11.5	0.061	26	
United States	77.3	47.3	0.717*	77.1	75.0	0.050	93	

Figure S1: Covariate balance measured by standardized differences in the propensity matched and unmatched cohorts



We planned to perform an analysis using propensity stratification, however, given the small sample size and small number of observations within strata, we were unable to successfully perform this analysis due to issues with convergence in the outcome model.

In conclusion, all sensitivity analyses yielded similar treatment effect estimates, with no significant differences observed in the primary outcome. The findings strengthen the conclusions drawn from the primary analysis.