Prophylactic anticoagulants for people hospitalized with COVID-19: systematic review

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Dear Editor,

Venous and arterial thromboembolic complications affect 16 and 31–49 per cent of patients hospitalized with COVID-19 and in intensive care units (ICUs) respectively. Of these, 90 per cent have venous thromboembolism. Pulmonary complications can occur in half of surgical patients with COVID-19. These are associated with a 30-day mortality rate of 23.8 per cent[1]. Anticoagulants are used in the prevention and treatment of venous or arterial thromboembolic events[2–4]. However, adverse events, such as bleeding, may occur, and can have a significant impact on patient care[2–4]. A Cochrane systematic review[5] was performed to assess the effects of prophylactic anticoagulants for people hospitalized with COVID-19.

CENTRAL, MEDLINE, Embase, LILACS, IBECS, the Cochrane COVID-19 Study Register, and the medRxiv preprint database (Table S1) were searched on 20 June 2020. RCTs, quasi-RCTs, and cohort studies that compared prophylactic anticoagulants versus active comparators, placebo or no intervention for the management of people hospitalized with COVID-19 were included. The risk of bias was assessed for non-randomized studies (NRS) using ROBINS-I (Table S1), and the certainty of evidence using GRADE. The results were reported narratively.

The search yielded a total of 1148 citations (Fig. S1). After excluding 103 duplicates, 1045 unique citations were screened. A total of 991 citations were considered not relevant at this stage, leaving 54 for full-text reading. Twelve studies (11 reports) were excluded. Twenty-two studies (26 reports) are ongoing. Another 13 studies were considered not relevant after a full-text analysis. No RCTs or quasi-RCTs that met the inclusion criteria were identified. For this review, seven NRS (5929 participants, 8 reports) were found with available data for inclusion, three of which were available as preprints.

Seven retrospective NRS (5929 participants) were included. Six of these studies (5685 participants) compared anticoagulants (all types) versus no treatment (Table 1). Two studies reported a reduction in mortality, three studies reported no differences in mortality, and one study reported zero events in both intervention groups (critical risk of bias; very low-certainty evidence). Another retrospective NRS (244 participants) compared therapeutic-dose anticoagulants versus prophylactic-dose anticoagulants, and reported a reduction in all-cause mortality and a lower absolute rate of death in the therapeutic group (34.2 versus 53 per cent) (serious risk of bias; low-certainty evidence) (Table S2). Twenty-two ongoing studies (20 RCTs, 14 730 participants; 2 NRS, 997 participants) in hospital settings were also identified. Twelve ongoing studies plan to report mortality and six plan to report additional respiratory support. Thirteen studies are expected to be completed in December 2020 (6959 participants).

Therefore, there is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulants for people hospitalized with COVID-19. As there are 22 ongoing studies, more robust evidence will be added to this review in future updates.

A comprehensive systematic search of the literature was performed using standard Cochrane methods. The review authors believe that they identified all relevant studies that met the inclusion criteria. However, the possibility remains that some studies may have been missed, particularly in the grey literature. The review authors adhered to methods prespecified in the protocol in order to limit subjectivity and potential biases in the review process.

To prevent microvascular thrombosis, some clinicians use higher-dose anticoagulation rather than prophylactic dosing for inpatients with COVID-19. However, this practice is not supported by robust evidence. Although some practical guidelines address the management of prophylactic anticoagulation in people with COVID-19, all of these recommendations are based on

Table 1 Anticoagulants (all types) compared with no treatment for people hospitalized (ICU and ward) with COVID-19: summary of findings

Outcome	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
All-cause mortality	One study reported reduction in mortality by OR adjusted for confounding (58% reduction in chance of death; 2075 participants)	5685	⊕⊖⊖
Follow-up: range 8–28 days	One study reported reduction in mortality only in a subgroup of severely ill participants (HR 0.86, 0.82 to 0.89; 395 participants)	(6 retrospective NRS)	Very low[*†‡]
	Three studies reported no differences by adjusted OR (1.64, 0.92 to 2.92; 449 participants), unadjusted OR (1.66, 0.76 to 3.64; 154 participants) or adjusted RR (1.15, 0.29 to 2.57; 192 participants)		
	One study reported zero events in both intervention groups		
Need for additional respiratory support	No study measured this outcome		
Mortality related to COVID-19	No study measured this outcome		
Deep vein thrombosis	No study measured this outcome		
Pulmonary embolism	No study measured this outcome		
Major bleeding	One study reported 24 bleeding events (3%) in the intervention group and 38 (1.9%) in the control group (OR 1.62, 0.96 to 2.71)	2773 (1 retrospective NRS)	⊕⊕⊖⊖ Low[‡§]
Follow-up duration not reported			

Odds ratios (ORs), hazard ratios (HRs), and risk ratios (RRs) are shown with 95 per cent confidence intervals. GRADE Working Group grades of evidence: high certainty—the authors are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty—the authors are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty—the authors' confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect; very low certainty—the authors have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. [*]Downgraded one level owing to study limitations; overall critical/serious risk of bias across studies, especially related to confounding. [†]Downgraded one level owing to inconsistency; the authors decided not to pool data because of the heterogeneity of studies (especially differences in interventions). [‡]Downgraded one level owing to imprecision; narrative synthesis was conducted with imprecise estimates. [§]Downgraded one level owing to study limitations; overall serious risk of bias, especially related to confounding. NRS, non-randomized studies.

non-COVID-19 populations or low-quality COVID-19-related evidence.

Supplementary material

Supplementary material is available at *BJS* online.

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