Venous and Arterial Thrombosis in Ambulatory and Discharged COVID-19 Patients: A Systematic Review and Meta-analysis

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Abstract

Introduction   Venous and arterial thromboses are frequently observed complications in patients with severe novel coronavirus disease 2019 (COVID-19) infection who require hospital admission. In this study, we evaluate the epidemiology of venous and arterial thrombosis events in ambulatory and postdischarge patients with COVID-19 infection.

Materials and Method   EMBASE and MEDLINE were searched up to July 21, 2021, in addition to other sources. We included studies that assessed the epidemiology of venous and arterial thrombosis events in ambulatory and postdischarge COVID-19 patients.

Results   A total of 16 studies (102,779 patients) were identified. The overall proportion of venous thromboembolic events in all patients, that is, ambulatory and postdischarge, was 0.80% (95% confidence interval [CI]: 0.44–1.28), 0.28% (95% CI: 0.07–0.64), and 1.16% (95% CI: 0.69–1.74), respectively. Arterial events occurred in 0.75% (95% CI: 0.27–1.47) of all patients, 1.45% (95% CI: 1.10–1.86) of postdischarge patients, and 0.23% (95% CI: 0.019–0.66) of ambulatory patients. The pooled incidence rate estimates per 1,000 patient-days for VTE events were 0.06 (95% CI: 0.03–0.08) and 0.12 (95% CI: 0.07–0.19) for outpatients and postdischarge, respectively, whereas for arterial events were 0.10 (95% CI: 0–0.30) and 0.26 (95% CI: 0.16–0.37).

Keywords
► thrombosis
► ambulatory
► outpatients
► postdischarge
► COVID-19

Conclusion   This study found a low risk of venous and arterial thrombi in ambulatory and postdischarge COVID-19 patients, with a higher risk in postdischarge patients compared with ambulatory patients. This suggests that regular universal thromboprophylaxis in these patient populations is probably not necessary.

Introduction

Novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) leads to endothelial and coagulation dysfunction which puts patients at an increased risk of both venous and arterial thrombotic events and also increases the morbidity and mortality associated with the disease.[1] Hospitalized COVID-19 patients are at a particularly high risk of thrombosis with estimates of venous thromboembolism (VTE) risk up to 8% in hospitalized patients and 24% in patients admitted to intensive care, according to two large systematic reviews.[2,3] Arterial events are estimated to occur in 1% of ward patients and 5% of critically ill patients.[4] However, the majority of published studies have focused on the incidence of thromboembolism during hospitalization, and it is unclear what the thrombotic risk is in outpatients who have a milder illness and do not require hospitalization and among patients who have been discharged after hospitalization for COVID-19 infection. This information could be helpful in deciding the need for thromboprophylaxis in these patient populations.

Methods

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (►Fig. 1) and is registered in PROSPERO (*https://www.crd.york.ac.uk/PROSPERO*; registration number: CRD42021292010).
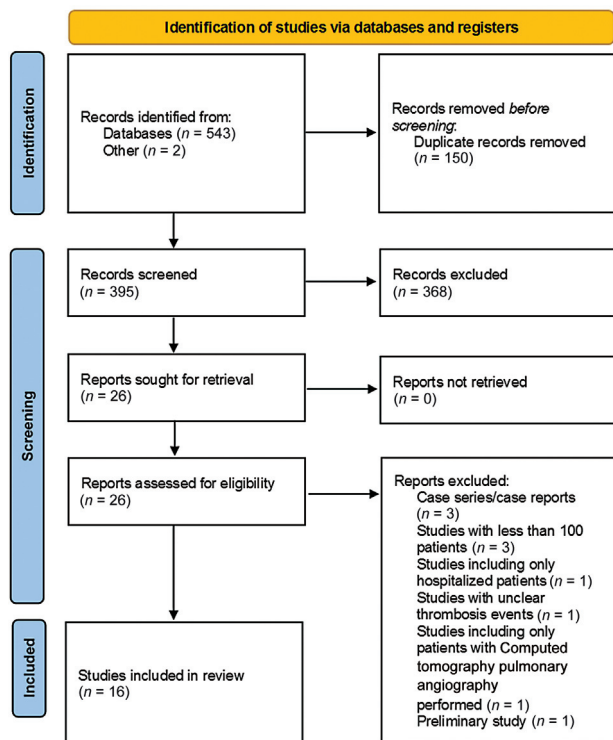

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for study selection. CTPA, computed tomography pulmonary angiography.

The literature search was performed using EMBASE and MEDLINE using medical subject headings and free text words through Boolean operators. The retrieved papers were also scanned for additional references in addition to searching preprint databases (*preprints.org, biorxiv.org*) for accepted papers not yet published. Full details on the search strategies of the main databases can be found in the ►**Supplementary Material S1**.

We included studies that looked at venous or arterial events in adult patients with COVID-19 either postdischarge, following hospitalization or ambulatory with no history of hospitalization. Full-text articles, abstracts, letters, brief reports, editorials, and correspondence were eligible for inclusion if they reported on randomized control trials (RCTs), observational cohort studies (prospective or retrospective), or case-control studies. We excluded studies with no original data, studies with less than 100 patients and studies that would not reflect the general risk of thrombosis in COVID-19 patients (e.g., studies that only included patients with computed tomography pulmonary angiogram (CTPA). There was no language restriction.

We conducted an initial broad screening according to title and reviewed all abstracts judged to be relevant. Potentially relevant papers were reviewed in total length. Articles were independently assessed by two reviewers (E.M.M. and M.A.-F) to verify eligibility and decide on inclusion vs exclusion. Disagreements were resolved by consensus or in conjunction with a third reviewer (A. L.-L.). Translation of included papers from Dutch to English was conducted using Google Chrome's built-in translation tool.

We extracted data on study characteristics, study methodology (including sample size, study design, health care setting, and ultrasound screening strategy), patients and diseases (hospitalization, thrombosis risk factors, and thromboprophylaxis strategy), and outcomes including (venous thromboembolism or arterial thrombosis.

The study aimed to look at the proportion of venous thromboembolism (i.e., deep venous thrombosis and pulmonary embolism) or arterial thrombosis in outpatients or postdischarge patients with COVID-19 infection as the primary outcome. We used the proportion of patients diagnosed with a thrombotic event in the included studies (prevalence) to compensate for the differences in event reporting between studies. Some studies used prevalence, while others used incidence rates depending on the study type. If needed, authors were contacted to obtain missing data. Additionally, we also estimated incidence rates if possible.

The quality and risk of bias of included observational studies were assessed using the Newcastle–Ottawa Scale (NOS) to evaluate the quality of nonrandomized studies in meta-analyses.[5] For randomized trials, we planned to use the Jadad scale.[6]

Statistical Analysis

A meta-analysis of proportions was done for the frequency of VTE and arterial thrombosis. We estimated pooled

proportions through a Freeman–Tukey transformation, using fixed and random effects models. We also estimated incidence rates (IR) from imperfect data assuming no losses to follow-up for the reported observation periods. We applied standard methods to obtain 95% confidence intervals (CIs) for the IR that we used to estimate standard errors. We calculated pooled estimates for the IR using the generic inverse variance method.[7]

The reported pooled proportions were obtained by a random-effects model given statistical heterogeneity. Sensitivity analyses were performed according to setting (outpatients vs. postdischarge), thrombosis type (VTE vs. arterial), and study type (retrospective vs. prospective). Additionally, we conducted a meta-analysis of the relative risk for VTE for the studies that included both postdischarge and outpatients. Exploratory analyses were also conducted according to percentage of use of thromboprophylaxis (<20 vs. $>20\%$) and duration of follow-up in the study (<42 vs. >42 days). Heterogeneity between studies was evaluated using Cochrane Q and Higgins I^2 tests. Publication bias was assessed using Egger's tests and funnel plots. The analysis was done using Microsoft Excel 365 (Microsoft Corp. Redmond, Washington, United States) and MedCalc Statistical Software version 19.2.6 (MedCalc Software Ltd., Ostend, Belgium).

Results

Search Strategy and Included Studies
The database search included papers published up to July 21, 2021. The search produced 543 studies through Medline and Embase and an additional two articles from other sources. A total of 368 studies were excluded after title and abstract screening, and a total of 26 articles were reviewed in full text. Of those, 16 studies met our eligibility criteria and were included. The reasons for excluding studies are summarized in ►Fig. 1. All the included studies were cohort studies (11 retrospective and 5 prospective). All studies were in English except one study published in Dutch.[8]

The studies were conducted in North America (seven in the United States and one in Canada), Europe (three from the United Kingdom and one each from Norway, the Netherlands, Denmark, and Belgium), and there was one multicenter study. Ten studies reported events in postdischarge patients, three reported on outpatients, and three reported on both outpatients, and postdischarge. The follow-up duration in the studies ranged from 30 days up to 6 months.

Only one study performed regular VTE screening at 6-week postdischarge.[9] With regard to thromboprophylaxis, many studies used some form of thromboprophylaxis on an individual basis or according to risk scores.[10]

Characteristics of included studies are shown in ►Table 1. Details of the included papers and a detailed reference list can be found in the ►Supplementary Tables S1 and S2.

All estimates showed high statistical heterogeneity; therefore, we focused our analysis on the results of random effects estimates, although the fixed effects estimates are

Table 1 Characteristics of included studies

Characteristics	No of studies
Country	
North America	8
Europe	7
Multicenter study	1
Study design	
Prospective cohort	5
Retrospective cohort	11
Setting	
Outpatients only	3
Postdischarge only	10
Both	3
Events reported	
VTE events only	8
Both Venous and arterial	8
Thromboprophylaxis strategy	
Prophylaxis used	7
No prophylaxis used	9

Abbreviation: VTE, venous thromboembolism.

shown for completeness when appropriate. Funnel plots are included in the ►Supplementary Figs. S1 to S8.

Venous Thromboembolic Events
The results are summarized in ►Table 2. The 16 included studies reported on 102,779 patients diagnosed with COVID-19 infection treated as either outpatients (85,051) or post-hospital discharge (17,728). In total, 388 patients had a VTE event with a pooled prevalence estimate of 0.80% (95% CI:0.44–1.28; Q-test: $p < 0.0001$, $I^2 = 97.33\%$).

In the outpatient population, 141 patients developed a VTE event with a pooled prevalence estimate of 0.28% (95% CI: 0.07–0.64, $p < 0.0001$, $I^2 = 97.45\%$). Among the postdischarge patients, 247 developed a VTE event with a pooled prevalence estimate of 1.16% (95% CI: 0.69–1.73; Q-test: $p < 0.001$, $I^2 = 87.21\%$).

Prospective studies included 14,904 patients with a pooled VTE prevalence estimate of 1.37% (95% CI: 0.48–2.69; Q-test: $p < 0.001$, $I^2 = 94.75\%$) and retrospective studies included 87,875 patients with a pooled VTE prevalence estimate of 0.62% (95% CI: 0.25–1.14; Q-test: $p < 0.001$, $I^2 = 97.63\%$).

Estimates for the pooled IR of VTE and arterial events are shown in ►Table 3. Funnel and forest plots are included in the ►Supplementary Figs. S9 to S16. The estimated pooled IR for VTE events in outpatients was 0.06 (95%CI: 0.03–0.08) events per 1,000 patient-days of observation and the estimate for postdischarge patients was 0.12 (0.07–0.19).

A meta-analysis conducted for studies including both discharged patients and outpatients showed that, compared with the latter, the pooled relative risk of VTE among discharged

Table 2 Estimates of the proportion of venous and arterial thrombotic events in ambulatory and postdischarge patients with COVID-19 infection

Patient population	No. of total patients	Percentage of patients with VTE (%)	95% confidence interval
Venous thromboembolic events			
All patients	102,779	0.80	0.44–1.28
Postdischarge	17,728	1.16	0.69–1.74
Outpatients	85,051	0.28	0.07–0.64
Subanalysis according to study design			
Prospective studies	14,904	1.37	0.48–2.69
Retrospective studies	87,875	0.62	0.25–1.14
Arterial events			
All patients	20,187	0.75	0.27–1.47
Postdischarge	7,816	1.46	1.10–1.86
Outpatients	12,371	0.23	0.02–0.66
Subanalysis according to study design			
Prospective studies	13,889	0.71	0.01–3.09
Retrospective studies	6,298	0.78	0.34–1.39

Abbreviations: COVID-19, novel coronavirus disease 2019; VTE, venous thromboembolism.

patients was 3.87 (95% CI: 0.38–39.18; $p = 0.252$) with a high heterogeneity (Cochrane's $Q = 128.34$ ($p < 0.001$); Higgins' $I^2 = 96.88$ (95% CI: 94.82–98.13; ►**Fig. 2**). Additional comparisons according to study design showed that in prospective studies the relative risk for discharged patients compared with outpatients was 0.46 (95% CI: 0.12–1.72; $p = 0.246$; Q-test: $p = 0.498$; $I^2 = 0\%$; $n = 890$). In comparison, the relative risk reported in retrospective studies was 11.31 (95% CI: 0.57–224.85; $p = 0.112$; Q-test: $p < 0.001$, $I^2 = 98.23$; $n = 82,666$). Estimates of VTE events according to the reported percent of utilization of thromboprophylaxis in studies, as well as dura-tion of follow-up showed similar results among groups (►**Supplementary Table S3**).

Arterial Events

Studies that evaluated arterial events included a total of 20,187 patients (including both outpatients and postdischarge) with an overall proportion of arterial events of 0.75 (95% CI: 0.27–1.47; Q-test: $p < 0.001$, $I^2 = 94.52\%$). In the outpatient population (12,371 patients) arterial thromboses occurred in 0.23% (95% CI: 0.019–0.66; Q-test: $p < 0.001$, $I^2 = 88.85\%$). Among 7,816 postdischarge patients,

Table 3 Pooled estimates for incidence rate of venous and arterial thrombotic events in ambulatory and postdischarge patients with COVID-19 infection

	IR (events per 1000 patient-days)		Heterogeneity	
	IR	95% CI	Q-test (p)	Higgins I^2 (%)
Venous thromboembolic events (outpatients)				
Fixed effects	0.02	0.02–0.03	<0.001	95.5
Random effects	0.06	0.03–0.08		
Venous thromboembolic events (postdischarge)				
Fixed effects	0.06	0.04–0.07	<0.001	82.7
Random effects	0.12	0.07–0.19		
Arterial events (outpatients)				
Fixed effects	0.01	0–0.01	0.001	93.2
Random effects	0.10	0–0.30		
Arterial events (postdischarge)				
Fixed effects	0.21	0.17–0.25	0.182	35.8
Random effects	0.26	0.16–0.37		

Abbreviations: CI, confidence interval; COVID-19, novel coronavirus disease 2019; IR, incidence rates.
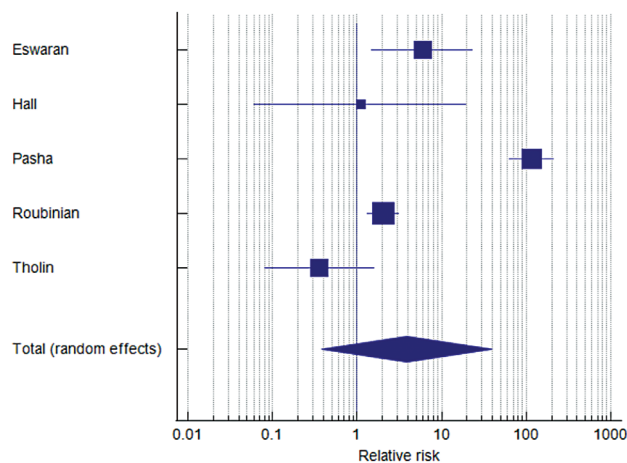
Fig. 2 Forest plot for the risk of venous thromboembolism in discharged patients compared with outpatients. Forest plot showing the pooled relative risk estimate of VTE for COVID-19 patients discharged from hospital compared with outpatients. The pooled relative risk was 3.87 (95% CI: 0.38–39.18; $p = 0.252$) with a high heterogeneity (Cochrane's Q = 128.34 [$p < 0.001$]; Higgins' $I^2 = 96.88$ (95% CI: 94.82–98.13). CI, confidence interval; COVID-19, novel coronavirus disease 2019; VTE, venous thromboembolism.

arterial events occurred in 1.46% (95% CI: 1.10–1.86; Q-test: $p = 0.242$, $I^2 = 25.57$%).

Retrospective studies included 6,298 patients with a pooled proportion of arterial events of 0.77% (95% CI: 0.34–1.39; Q-test: $p = 0.001$, $I^2 = 77.81$%), while prospective studies included 13,889 patients with a pooled proportion of arterial events of 0.71% (95% CI: 0.01–3.09; Q-test: $p < 0.0001$, $I^2 = 99.11$%).

Estimates for the pooled IR of arterial events per 1,000 patient-days of observation were 0.10 (95%CI: 0–0.303) in outpatients and 0.26 (95% CI: 0.16–0.37) in postdischarge patients, respectively. Given a lack of data, we were unable to conduct a meta-analysis comparing discharged patients to outpatients.

Discussion

Hospitalization for COVID-19 infection is associated with an increased risk of thrombosis,[2,3] but whether the COVID-19 infection increases the risk of VTE outside of the hospital setting is not well established. In this systematic review, we found that patients with COVID-19 infection not severe enough to require hospitalization or those, who are discharged and not in the acute phase anymore, do not have a markedly increased risk of thrombosis, both venous and arterial and in the case of postdischarge patients, their risk might be similar to other medically ill outpatients after hospital discharge. The MARINER trial looked at the benefit of using Rivaroxaban 10 mg. daily for thromboprophylaxis after hospital discharge in medical patients at high risk of VTE based on a score of ≥4 in the modified IMPROVE-VTE score or ≥2 plus D-Dimer level > 2 ULN (upper limit of normal) at discharge. In this study, the occurrence of symptomatic VTE in the placebo and intervention groups were 1.10 and 0.83%, respectively.[11] For comparison, the occur-

rence of VTE events is more than double (up to 2.8%) in patients undergoing major orthopedic surgery which is an accepted indication for anticoagulant prophylaxis.[12] More recently, the benefit of anticoagulant prophylaxis to reduce mortality in populations at risk for VTE has been questioned as the use of anticoagulants is associated to a higher risk of bleeding counterbalancing the relevance of VTE prevention.[13] Furthermore, our results showed that compared with fully ambulatory patients, the relative risk for VTE among discharged patients was not statistically significant, despite being numerically higher. Additionally, exploratory analyses showed similar proportion of VTE in patients according to the reported proportion of use of thromboprophylaxis in individual studies. These and the previously mentioned findings are important, since the use of anticoagulant prophylaxis in all these patients would be of doubtful benefit with the reported rates of events and uncertainty about the increased risk of VTE, and it would likely result in a higher risk of bleeding complications.

The findings of our review are consistent with other reports and expand on the information reported by another systematic review that also looked at the risk of VTE in postdischarge COVID-19 patients and reported a VTE risk of 1.8% (95% CI: 0.8–4.1%, $I^2 = 96.0$%),[14] in agreement with our findings. We believe that the difference in calculated risk stems from including two recent large cohorts in our systematic review that were not included in the previous one.[15,16] Additionally, our study reports on pooled estimates of incidence rates which also demonstrate a low IR of venous and arterial events.

Although some studies comparing COVID-19-positive with COVID-19-negative patients have reported a higher risk of thrombosis in COVID-19 patients compared with other medical patients, the results were not statistically significant. One study assessed the occurrence of postdischarge VTE in patients with COVID-19 compared with a 2019 control cohort and reported an odds ratio (OR) of 1.6 (95% CI: 0.8–3.1).[17] Another study that looked at the incidence of complications in the post–acute phase of SARS-CoV-2 infection in outpatients, comparing SARS-CoV-2-positive with SARS-CoV-2-negative individuals, found the VTE risk to be slightly higher in COVID-19 infection with 0.2 versus 0.1% (risk difference = +0.1% [95% CI: 0.0–0.2]; risk ratio = 1.77 [95% CI: 1.09–2.86]).[18] Pasha et al showed that the incidence of VTE increased within the first week following positive COVID-19 testing and the rate then decreased and returned to baseline by the sixth week; however, in this study, only 3% of VTE events occurred in patients who were never hospitalized.[15] In ambulatory patients, a randomized trial including 657 symptomatic outpatients with COVID-19 evaluated the use of different thromboprophylaxis strategies compared with placebo.[19] The study was terminated early because of a very low event rate. Among randomized participants who were on aspirin (81-mg once daily), apixaban (2.5-mg twice daily), apixaban (5.0-mg twice daily), or placebo, the rates of composite outcomes (including symptomatic venous or arterial thromboembolism, or hospitalization for cardiac or pulmonary cause) after 45 days were 0.0, 0.7, 1.4, and 0.0%, respectively, with no significant differences between the

active groups and the placebo group. Interestingly, a study on outpatients with COVID-19 who were on outpatient anticoagulation at the time of diagnosis reported a reduction in the risk of hospitalization but not mortality.[20]

It is estimated that arterial events complicate 3.9% of COVID-19 admissions, although the amount of literature concerning arterial events is more limited.[21] Similarly, the burden in non-COVID-19 patients is unknown. A study investigating the rates of myocardial infarctions and stroke following hospital admission for pneumonia found an incidence of 2.5% for myocardial infarction and 0.2% for stroke.[22] The estimate for the risk of cardiovascular events in general medically ill outpatients was unclear.

It has been suggested that the administration of low molecular weight heparin during the earlier phases of COVID-19 infection may be beneficial not only in the prevention of thrombosis risk but also in reducing systematic and pulmonary inflammation and limiting viral invasion.[23,24] A randomized controlled trial, the OVID trial (ClinicalTrials.gov Identifier: NCT04400799), is currently being conducted. This study aims to evaluate whether prophylactic-dose enoxaparin (vs. no treatment) can decrease early all-cause mortality and subsequent hospitalizations in adult symptomatic ambulatory COVID-19 patients with no other indications to receive anticoagulation.[25]

The use of thromboprophylaxis in postdischarge patients has been explored previously in patients with medical illness by the MARINER trial which showed no reduction in the risk of symptomatic venous thromboembolism and death due to venous thromboembolism compared with placebo.[11] A recent randomized control study applied the IMPROVE-VTE score on discharged patients posthospitalization with COVID-19 and reported that high-risk patients with a score of ≥4, or 2 to 3 with a D-dimer >500 ng/mL, had improved outcomes when on thromboprophylaxis with rivaroxaban 10 mg/day for 35 days.[26] This study used a composite outcome including symptomatic, asymptomatic, and fatal VTE (all detected by mandatory screening), as well as arterial thromboembolism including myocardial infarction, stroke, adverse limb events, and cardiovascular death. The generalizability of these findings is questionable for several reasons. The study accrued only 30% of potentially eligible patients, and more than half of the patients in this study had been admitted to the intensive care unit suggesting that the population included a larger than usual proportion of patients with severe disease. Additionally, the reported proportion of events in this study amounted to near 10% in the control arm which is not in agreement with large observational studies suggesting that the included population in the trial was a higher risk one. However, the findings of the trial raise the question about the need to identify specific subpopulations of patients at a higher risk of postdischarge VTE and that might benefit from thromboprophylaxis.

Current guidelines suggest against (1) using thromboprophylaxis in medical outpatients with no major provoking risk factors for VTE, and (2) using extended-duration outpatient VTE prophylaxis in the case of discharged patients.[27] Most importantly, the American College of Chest Physicians (ACCP) and the American Society of Hematology recommen-

dations suggest that routine extended thromboprophylaxis after hospital discharge of COVID-19 patients may not have a net clinical benefit.[28,29]

Our findings support these recommendations as the proportion and incidence of venous and arterial thrombosis observed in our study are similar to the reported risk of bleeding associated with the use of thromboprophylaxis, in addition to the added burden and cost. This aligns with the findings of a study by Giannis et al who reported that patients discharged on anticoagulation had a major bleeding rate of 2.45% compared with 1.63% in those who were discharged without any anticoagulation.[10] Therefore, the decision to use thromboprophylaxis should not be influenced by COVID-19 status but should be based on an overall assessment of patients' thrombosis risk factors balanced with their bleeding risk, although a precise and proven algorithm to assess these risks is currently not available.

Limitations

A limitation to this meta-analysis is that the included studies for postdischarge patients had different rates of patients on prophylactic anticoagulation ranging from 0 to 97%, but in general, there was only a small percentage of high-risk discharged patients started on prophylactic anticoagulation, but no clear criteria were used. Given the heterogeneity in approaches, subgroup analyses might be misleading and and need to be interpreted with much caution. Additional limitations to our study are those inherent to the included reports, mainly the fact that the majority of patients were included in retrospective studies. However, the proportion of events was almost double in prospective studies compared with retrospective ones, suggesting the possibility of recall bias, although the overall incidence is still very low even considering the possibility of events underreporting. Additionally, the estimate of IR needs to be interpreted with caution, as it was conducted under the assumption of no losses to follow-up which is unlikely to be the case. However, given the short observation period (less than 42 days in 11 of 16 studies) losses to follow-up are likely low and would result in marginal modifications to the estimates. In any case, the proportions of events were similar in studies with shorter or longer follow-up. Another issue is the potential for COVID-19 vaccines to influence the risk of VTE. In this regard, most recent studies have reported no influence of vaccines on the incidence of VTE,[30,31] except perhaps for the ChAdOx1 vaccine,[32] but overall it seems that vaccines are safe in this regard. This information was not available in the studies included in this review. Finally, although statistical heterogenicity was found between studies, all the proportion estimates were very low, and there was no evidence of publication bias for most outcomes (►Supplementary Table S4).

Conclusion

In conclusion, our findings suggest that patients with COVID-19 infection not severe enough to require hospitalization and those who are postdischarge and past the acute phase are not at a particular high rate of thrombosis, and their thrombosis

risk is similar to other patients with medical illness. We believe that these findings support the current recommendations, suggesting that prophylactic anticoagulation should not be routinely prescribed in these groups of patients. However, to better inform clinical decisions, further research is needed to define subgroups that could potentially benefit from anticoagulant prophylaxis by identifying those patients at a high risk of postdischarge thrombosis and a low bleeding risk that would derive the most benefit from this intervention.

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Conflict of Interest
None declared.

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