Venous Thromboembolism and Major Bleeding in Patients With Coronavirus Disease 2019 (COVID-19): A Nationwide, Population-Based Cohort Study

Michael Dalager-Pedersen,1,2 Lars Christian Lund,3 Theis Mariager,1 Rannva Winther,4 Maja Helffritsch,4 Torben Bjerregaard Larsen,5,6 Reimar Wennich Thomsen,7 Nanna Borup Johansen,7 Ole Schmelzt Segaad,8 Stig Lenberg Nielsen,9,10 Lars Haualki Omland,11 Lene Fogt Lundbo,11 Simone Bastrup Israelsen,11,12 Zitta Barrella Harboe,14 Anton Pottegård,3 Henrik Nielsen,1,2 and Jacob Bodilsen1,4

1Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark; 2Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; 3Clinical Pharmacology and Pharmacy, University of Southern Denmark, Odense C, Denmark; 4Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus C, Denmark; 5Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; 6Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark; 7Department of Clinical Evaluation and Biostatistics, Danish Medicines Agency, Copenhagen, Denmark; 8Department of Infectious Diseases, Aarhus University Hospital, Aarhus N, Denmark; 9Department of Infectious Diseases, Odense University Hospital, Odense C, Denmark; 10Research Unit for Infectious Diseases, Odense University Hospital, Odense, Denmark; 11University of Southern Denmark, Odense, Denmark; 12Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; 13Center of Research & Disruption of Infectious Diseases (CREDID), Department of Infectious Diseases, Copenhagen University Hospitals, Hvidovre, Denmark; and 14Department of Pulmonary Medicine and Infectious Diseases, Copenhagen University Hospital North Zealand, Hillerød, Denmark

Background. Venous thromboembolism (VTE) is a potentially fatal complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and thromboprophylaxis should be balanced against risk of bleeding. This study examined risks of VTE and major bleeding in hospitalized and community-managed SARS-CoV-2 patients compared with control populations.

Methods. Using nationwide population-based registries, 30-day risks of VTE and major bleeding in SARS-CoV-2 positive patients were compared with those of SARS-CoV-2 test-negative patients and with an external cohort of influenza patients. Medical records of all COVID-19 patients at 6 departments of infectious diseases in Denmark were reviewed in detail.

Results. The overall 30-day risk of VTE was 0.4% (40/9460) among SARS-CoV-2 patients (16% hospitalized), 0.3% (649/226,510) among SARS-CoV-2 negative subjects (12% hospitalized), and 1.0% (158/16,281) among influenza patients (59% hospitalized). VTE risks were higher and comparable in hospitalized SARS-CoV-2 positive (1.5%), SARS-CoV-2 negative (1.8%), and influenza patients (1.5%). Diagnosis of major bleeding was registered in 0.5% (47/9460) of all SARS-CoV-2 positive individuals and in 2.3% of those hospitalized. Medical record review of 582 hospitalized SARS-CoV-2 patients observed VTE in 4% (19/450) and major bleeding in 0.4% (2/450) of ward patients, of whom 31% received thromboprophylaxis. Among intensive care patients (100% received thromboprophylaxis), risks were 7% (9/132) for VTE and 11% (15/132) for major bleeding.

Conclusions. Among people with SARS-CoV-2 infection in a population-based setting, VTE risks were low to moderate and were not substantially increased compared with SARS-CoV-2 test-negative and influenza patients. Risk of severe bleeding was low for ward patients, but mirrored VTE risk in the intensive care setting.

Keywords. COVID-19; venous thromboembolism; pulmonary embolism; deep venous thrombosis; hemorrhage; bleeding.
METHODS

Setting
The study was conducted in Denmark where all ~5,800,000 inhabitants are provided with universal, tax-supported health-care, free of charge at the point of delivery. All residents are assigned a unique 10-digit civil registration system (CRS) number, which is used for all health-care contacts, including hospitalizations and prescription medicine, and facilitates individual-level linkage between nationwide Danish registries [12]. The study period was January 27 to June 1, 2020. As of April 21, 2020, the SARS-CoV-2 test strategy in Denmark changed from examining only symptomatic persons to testing all patients admitted to hospital >24 h and asymptomatic individuals potentially exposed for SARS-CoV-2 (Supplementary Material) [13]. All clinical tests for SARS-CoV-2 during the study period were analyzed at departments of clinical microbiology using reverse-transcriptase polymerase-chain-reaction (PCR). On April 17, 2020, the Danish Society of Thrombosis and Hemostasis introduced a guideline on thromboprophylaxis of COVID-19 patients suggesting intermediate doses of low-molecular weight heparin (LMWH) to ICU patients and low dose LMWH to all ward patients.

Data Sources
Data sources for this study included nationwide, population-based administrative health registries combined with electronic medical record (EMR) review in a subgroup of patients (Figure 1).

Established in 1967, the CRS database was used for information on date of birth, sex, and migration and vital status for all study subjects with <0.3% lost to follow-up [12]. The Microbiological Database (MiBa) was used to identify all patients with SARS-CoV-2 confirmed by PCR assays performed on upper or lower respiratory tract specimens [14]. It has received real-time reports from all departments of clinical microbiology in Denmark since 2010. MiBa was also accessed to identify patients with a negative test for SARS-CoV-2. The National Patient Registry was used for information on all hospital admissions, comorbidity, VTE, and bleeding events (Supplementary Table 1) [15]. It keeps record of complete WHO International Classification of Diseases (ICD) diagnosis codes on all inpatient hospitalizations since 1977 and outpatient hospital contacts in Denmark since 1995. For each hospitalization, a treating physician assigns one primary discharge diagnosis code for the condition that prompt hospitalization, and mainly affects treatment course, and up to 20 secondary codes. The National Prescription Registry holds data on reimbursed prescriptions at community pharmacies by Anatomical Therapeutic Chemical (ATC) codes since 1995 [16]. It was accessed to obtain data on medication use before hospital admission and after discharge (Supplementary Table 1).

Figure 1. Characteristics of study populations, covariate time windows, and follow-up time. Abbreviations: COVID-19, coronavirus disease 2019; MiBa, Microbiological Database; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
In addition, EMRs of all COVID-19 patients treated at departments of infectious disease at Aarhus, Odense, Hvidovre, Rigshospitalet (Copenhagen), Hillerød, and Aalborg university hospitals were reviewed. Clinical data were extracted including data on comorbidities, medication use before and during admission, tobacco and alcohol habits, signs and symptoms at admission, laboratory tests, radiological examinations, and occurrence of VTE or major bleeding events. These data were managed using Research Electronic Data Capture browser-based software (REDCap, Vanderbilt, TN, USA).

Study Cohorts
First, using health-care registries, a cohort comprising all cases of SARS-CoV-2 infection Denmark, diagnosed until May 1, 2020 was assembled. Second, because VTE risk may be related to acute illness in general rather than pathophysiological effects of SARS-CoV-2 per se, a comparison cohort comprising all nonhospitalized and hospitalized patients who tested negative for SARS-CoV-2 (and remained test-negative) until May 1, 2020 was identified. Third, as an additional point of comparison, an external cohort of adults born before 1978 with laboratory-confirmed influenza from 2010 through 2018 was used to examine if SARS-CoV-2 confers a greater VTE risk than another serious viral respiratory infection [17].

For increased clarity on diagnostic exams and in-hospital management of COVID-19 patients, EMRs of all patients hospitalized with laboratory-verified SARS-CoV-2 at 6 departments of infectious diseases in Denmark from February 27, 2020 (day of first Danish patient diagnosed with COVID-19) through May 4, 2020, were reviewed.

Outcome Events
In the registry-based cohort analyses, VTE and major bleeding events were defined as any discharge diagnosis code made either during index-hospitalization (for patients already hospitalized on date of microbiological testing) or during new hospitalization within 30 days after microbiological testing. In an additional analysis including prescription data, VTE was defined by either a diagnosis code for VTE or a post-discharge reimbursed prescription for new anticoagulant therapy likely due to VTE, as indicated by an algorithm based on relevant ATC codes (Supplementary Table 2).

In the EMR cohort analysis, VTE was defined as a deep vein thrombosis (DVT) diagnosed by compression ultrasound or pulmonary embolism (PE) diagnosed by CT pulmonary angiography or lung scintigraphy according to the radiologist’s description. Date of VTE was categorized as the day of diagnostic imaging. Major bleeding events were defined as 1) any diagnosis of central nervous system, retroperitoneal or intraocular bleeding, 2) clinical bleeding requiring transfusion of >1 unit of blood, or significant medical or surgical intervention, 3) bleeding significantly contributing to death as judged by the treating physician.

Statistics
Categorical variables were presented as numbers and percentages with 95% confidence intervals (CI) and continuous variables as medians with interquartile ranges (IQR). Covariate balances were examined using standardized mean differences. No patients had missing data on exposure or primary outcome and the primary analyses included all study participants.

The date of microbiological testing was defined as cohort entry (index) date. Individuals were excluded if they had either VTE during the year prior to microbiological testing, less than 1 year of enrollment in the database prior to test date, or emigrated out of the country less than 30 days after sample date. All study subjects in registry-based cohorts were followed from the index date until completion of 30 days of follow-up, death or June 1, 2020, whichever came first.

For each study cohort, 30-day absolute risks of VTE, major bleeding events, and mortality were computed. Subgroup analyses were performed by age group (0–64, 65+ years of age), sex, presence of risk-factors for VTE (yes/no), and Charlson Comorbidity Index (CCI of 0 and CCI ≥ 1) [18]. A limited number of primary outcomes among SARS-CoV-2 positive patients precluded planned adjusted analyses of relative risk.

Subjects in the EMR cohort were followed from date of SARS-CoV-2 test until date of VTE, major bleeding, death, emigration out of Denmark, or date of last medical record review (May 4), whichever came first. Next, 30-day risks of VTE, bleeding, and mortality were computed and stratified by ICU admission (yes/no). In non-ICU patients, risk estimates were further examined by receipt of anticoagulant therapy (all ICU patients received at least standard dose thromboprophylaxis).

Stat 16.1 (Stata Corp., College Station, TX) was used for all analyses.

Ethics
The study was approved by the Danish Board of Health (ID: 31–1522–84) and registered at the University of Southern Denmark (ID: 10.960) and the legal authorities in North Denmark Region (ID: 2020–045). Thus, patient consent or approval from an ethical committee was not required for this study in Denmark.

RESULTS
Registy-Based Cohorts
Data retrieval from Danish registries yielded 9460 SARS-CoV-2 positive patients between February 27 and May 4, 2020 (1540 hospitalized; 16%), and 226 510 SARS-CoV-2 negative patients in the same period (26 131 hospitalized; 12%). Between 2010 and 2018, we identified 16 281 patients tested positive with influenza (9599 hospitalized; 59%). Among hospitalized patients, median age and proportion of males were 72 years (IQR 58–81)
and 57% (872/1540) for SARS-CoV-2 positive patients, 68 years (48–78) and 50% (13 100/26 131) for SARS-CoV-2 negative individuals, and 70 years (59–80) and 51% (4688/9599) for influenza patients (Table 1). Presence of comorbidity (CCI > 0) at admission was found in 36% (558/1540) of hospitalized SARS-CoV-2 positive patients, 38% (10 035/26 131) of hospitalized SARS-CoV-2 negative individuals, and 49% (4717/9599) of hospitalized influenza patients.

Overall 30-day risk for VTE was 0.4% (40/9460) among SARS-CoV-2 positive patients compared with 0.3% (649/226 510) for SARS-CoV-2 negative patients and 1.0% (158/16 281) among influenza patients. In hospitalized patients, risks for VTE were 1.5% (23/1540) in SARS-CoV-2 positive patients compared with 1.8% (483/26 131) in SARS-CoV-2 negative patients and 1.5% (147/9599) in hospitalized influenza patients (Tables 2 and 3). In additional analyses using both discharge diagnoses and prescription data to confirm VTE, risk of VTE increased to 2.3% (36/1540) in hospitalized SARS-CoV-2 positive patients, and 2.2% (576/26 131) in hospitalized SARS-CoV-2 negative patients. For all cohorts, risk for PE was approximately 3-fold greater than the risk for DVT.

Major bleeding events among hospitalized study participants occurred in 2.3% (36/1540) of SARS-CoV-2 positive patients, 4.5% (1170/26 131) of SARS-CoV-2 negative individuals, and 2.4% (234/9599) in hospitalized influenza patients.

Thirty-day mortality was 5.5% (523/9460) among individuals with a positive test for SARS-CoV-2, 1.3% (2946/226 510) in SARS-CoV-2 negative patients, and 5.7% (932/16 281) in influenza patients.

**EMR Cohort**

During the study period, 582 patients were treated for SARS-CoV-2 at 6 departments of infectious disease in Denmark (Table 4). The median age was 69 years (54–78) and 58% were male (335/582). At least 1 pre-existing risk factor for VTE was observed in 22% of patients (130/582) with body mass index >35 kg/m² as the most frequent (8%; 49/582). Median duration of COVID-19 symptoms before admission was 7 days (IQR 4–10) and common symptoms included history of fever in 82% (445/542), cough in 77% (417/543), and dyspnea in 70% (373/535) of patients. Blood tests at admission showed a median C-reactive protein level of 57 mg/L (IQR 29–120) and D-dimer of 0.87 mg/L (IQR 0.49–1.50). Radiological examinations included chest x-ray in 94% (545/582) of patients, computed tomography of the chest in 13% (76/582), and compression ultrasound of lower extremities in 3% (16/582). In total, 23% (132/582) of patients were admitted to ICU and 19% (109/582) were mechanically ventilated.

Anticoagulant therapy was used in 31% (140/450) of ward patients and 100% (132/132) of ICU patients during admission, primarily as prophylactic dose low-molecular weight heparin (Table 5). Overall, VTE occurred in 5% (28/582) of hospitalized patients after exclusion of 5 patients with a presumptive diagnosis of PE but without radiological confirmation. Major bleeding was observed in 3% (17/582) and 20% (124/582) had a fatal outcome. Risk of VTE was 4% (19/450) among ward patients and 7% (9/132) among patients admitted at the ICU.

For ward patients receiving thromboprophylactic therapy, VTE occurred in 3% (4/140) and major bleeding was observed in 1% (2/140) patients. For ward patients not treated with thromboprophylaxis, VTE was found in 5% (15/310) and major bleeding in 0% (0/310) patients. All patients admitted at the ICU received anticoagulant therapy and major bleeding was observed in 11% (15/132).

**DISCUSSION**

In this Danish nationwide, population-based cohort study, 30-day risk of VTE was 0.2% among nonhospitalized and 1.5% in hospitalized SARS-CoV-2 patients (2.3% when adding prescription data). In comparison, major bleeding events occurred in 0.1% of nonhospitalized and 2.3% of hospitalized SARS-CoV-2 positive patients. Risks of VTE and major bleeding were slightly higher by medical record review and were comparable with those of SARS-CoV-2 negative individuals and influenza patients.

Studies addressing VTE risk in SARS-CoV-2 are mostly limited by small or moderate sample sizes from single- or a few centers with selected patient populations and incomplete follow-up [3–10]. In addition, some studies used VTE screening and included asymptomatic VTEs and subsegmental PE, both of which are of uncertain clinical relevance [19]. Consistent with the current study, several other studies have found VTE risks of 3%–7% among ward patients and 7%–8% in ICU patients [10, 20–23]. In contrast, VTE was observed in 3% of non-ICU patients and in 23%–35% of ICU patients in two Dutch studies where VTE screening and thromboprophylaxis was standard [4, 8]. Another 2 ICU studies observed risks of VTE of 17%–21% in SARS-CoV-2 patients compared with 8% in influenza patients and 1% in a heterogeneous group of ARDS patients [6, 9]. In comparison, relatively few cases of VTE were diagnosed in the current study despite more restricted use of thromboprophylaxis. Reasons for the large discrepancy in VTE risk between studies are unclear. Among hospitalized patients in the current study, VTEs may have gone undetected either through lack of clinical suspicion or due to barriers in performing diagnostic exams such as chest CTs in mechanically ventilated ICU patients. Still, mortality rates among hospitalized COVID-19 patients in our study were comparable with or lower than other studies, suggesting that missed fatal VTEs were limited [10, 21–23]. Moreover, difficulty with diagnostic imaging is unlikely to explain the observed low risk estimates in nonhospitalized patients and non-ICU patients, and compression ultrasound is relatively easy to perform and DVT was rarely diagnosed.
Table 1. Registry-Based Analyses of Baseline Characteristics for SARS-CoV-2 Positive, SARS-CoV-2 Negative, and Influenza Patients (n/N, % or Median With Interquartile Ranges [IQR])

<table>
<thead>
<tr>
<th></th>
<th>Nonhospitalized</th>
<th>SMD (SARS+ v. SARS-)</th>
<th>Hospitalized</th>
<th>SMD (SARS+ v. SARS-)</th>
<th>Influenza patients</th>
<th>SMD (Influenza v. SARS+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (% of n)</td>
<td>7920 (83.7)</td>
<td>200379 (88.5)</td>
<td>6682 (41.0)</td>
<td>1540 (16.3)</td>
<td>26131 (11.5)</td>
<td>9599 (59.0)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>46 (32–58)</td>
<td>45 (31–58)</td>
<td>55 (46–67)</td>
<td>0.10</td>
<td>58 (58–81)</td>
<td>0.14</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>4825 (60.9)</td>
<td>130171 (65.0)</td>
<td>3696 (55.3)</td>
<td>0.08</td>
<td>100 (50.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Charlson score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7141 (90.2)</td>
<td>179086 (89.4)</td>
<td>5368 (80.3)</td>
<td>0.03</td>
<td>6969 (81.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>1–2</td>
<td>668 (8.4)</td>
<td>18416 (9.2)</td>
<td>1047 (15.7)</td>
<td>0.03</td>
<td>6999 (8.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>≥3</td>
<td>111 (1.4)</td>
<td>2877 (1.4)</td>
<td>267 (4.0)</td>
<td>0.00</td>
<td>3036 (4.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>VTE risk factors</td>
<td>1403 (17.7)</td>
<td>41321 (20.6)</td>
<td>1567 (23.5)</td>
<td>0.07</td>
<td>1790 (24.9)</td>
<td>0.00</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>194 (2.4)</td>
<td>4361 (2.2)</td>
<td>222 (3.3)</td>
<td>0.02</td>
<td>1997 (2.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Surgery</td>
<td>92 (1.2)</td>
<td>3321 (1.7)</td>
<td>187 (2.8)</td>
<td>0.04</td>
<td>3719 (4.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>129 (1.6)</td>
<td>2089 (1.0)</td>
<td>257 (3.8)</td>
<td>0.05</td>
<td>3560 (4.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Trauma</td>
<td>66 (0.8)</td>
<td>1744 (0.9)</td>
<td>50 (0.7)</td>
<td>0.00</td>
<td>1284 (1.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Active cancer</td>
<td>126 (1.6)</td>
<td>4378 (2.2)</td>
<td>265 (4.0)</td>
<td>0.04</td>
<td>3410 (4.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Obesity</td>
<td>623 (7.9)</td>
<td>19409 (9.7)</td>
<td>496 (7.4)</td>
<td>0.06</td>
<td>2930 (11.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>129 (1.6)</td>
<td>4322 (2.2)</td>
<td>72 (1.1)</td>
<td>0.04</td>
<td>1409 (5.4)</td>
<td>0.28</td>
</tr>
<tr>
<td>Dalsys</td>
<td>7 (0.1)</td>
<td>229 (0.1)</td>
<td>60 (0.9)</td>
<td>0.01</td>
<td>281 (1.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>24 (0.3)</td>
<td>778 (0.4)</td>
<td>19 (0.3)</td>
<td>0.01</td>
<td>102 (0.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>HRT</td>
<td>259 (3.3)</td>
<td>8337 (4.2)</td>
<td>374 (5.6)</td>
<td>0.05</td>
<td>1065 (4.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Other comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td>270 (3.4)</td>
<td>6561 (3.3)</td>
<td>0.01</td>
<td>404 (6.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>745 (9.4)</td>
<td>20569 (10.3)</td>
<td>1210 (18.1)</td>
<td>0.03</td>
<td>896 (12.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Heart failure</td>
<td>114 (1.4)</td>
<td>2872 (1.4)</td>
<td>231 (3.5)</td>
<td>0.00</td>
<td>2661 (3.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>MI</td>
<td>131 (1.7)</td>
<td>3517 (1.8)</td>
<td>255 (3.8)</td>
<td>0.01</td>
<td>2147 (3.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>379 (4.8)</td>
<td>10237 (5.1)</td>
<td>0.01</td>
<td>505 (7.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>COPD</td>
<td>178 (2.2)</td>
<td>6959 (3.5)</td>
<td>434 (6.5)</td>
<td>0.07</td>
<td>4241 (6.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Renal failure</td>
<td>88 (1.1)</td>
<td>2175 (1.1)</td>
<td>310 (4.6)</td>
<td>0.00</td>
<td>2138 (3.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Liver disease</td>
<td>94 (1.2)</td>
<td>2625 (1.3)</td>
<td>117 (1.8)</td>
<td>0.01</td>
<td>1121 (4.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Alcohol rel. disease</td>
<td>167 (2.1)</td>
<td>7753 (3.9)</td>
<td>176 (2.6)</td>
<td>0.10</td>
<td>2855 (10.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>Pre-existing antithrombotic use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2. Registry-Based Data of 30-Day Risks of VTE (n/n, %) in SARS-CoV-2 Test Positive or Negative Patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nonhospitalized</th>
<th></th>
<th>Hospitalized</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SARS-CoV-2</td>
<td>SARS-CoV-2</td>
<td>SARS-CoV-2</td>
<td>SARS-CoV-2</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>VTE (diagnoses only)</td>
<td>117/920 (0.2)</td>
<td>166/200 379 (0.1)</td>
<td>0.1 (95% CI)</td>
<td>0.0 to 0.2</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>5/920 (0.1)</td>
<td>79/200 379 (0.0)</td>
<td>0.0 (95% CI)</td>
<td>0.0 to 0.1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>12/920 (0.2)</td>
<td>87/200 379 (0.0)</td>
<td>0.1 (95% CI)</td>
<td>0.0 to 0.2</td>
</tr>
<tr>
<td>VTE (incl. prescriptions)</td>
<td>24/920 (0.3)</td>
<td>206/200 379 (0.1)</td>
<td>0.2 (95% CI)</td>
<td>0.1 to 0.3</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>11/920 (0.1)</td>
<td>474/200 379 (0.2)</td>
<td>-0.1 (95% CI)</td>
<td>-0.2 to 0.0</td>
</tr>
<tr>
<td>VTE in subgroups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>NA</td>
<td>90/159 058 (0.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>NA</td>
<td>76/41 321 (0.2)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>NA</td>
<td>86/730 171 (0.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>NA</td>
<td>8070 208 (0.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-64</td>
<td>10/6758 (0.1)</td>
<td>91/172 156 (0.1)</td>
<td>0.1 (95% CI)</td>
<td>0.0 to 0.2</td>
</tr>
<tr>
<td>65+</td>
<td>7/1162 (0.6)</td>
<td>75/28 223 (0.3)</td>
<td>0.3 (95% CI)</td>
<td>0.1 to 0.8</td>
</tr>
<tr>
<td>Charlson score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>NA</td>
<td>133/179 086 (0.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>NA</td>
<td>332/329 (0.2)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; incl., including; NA, not applicable as Danish regulations do not allow reporting of less than 5 individuals in each cell; SARS, severe acute respiratory syndrome; VTE, venous thromboembolism.

aNumbers refer to start of follow-up. A large number of patients were hospitalized at end of follow-up, 201 SARS-CoV-2 positive patients and 2712 SARS-CoV-2 negative patients.

bAmong hospitalized SARS-CoV-2 patients, VTE was diagnosed in 16/991 (1.6%) from February 27 through March 31 and in 7/549 (1.3%) from April 1 through April 30, 2020.
## Table 3. Registry-Based Data of 30-Day Risks of VTE (n/N, %) in SARS-CoV-2 Test Positive and Influenza Patients

| Outcome | Non-hospitalized | | | Hospitalized<sup>a</sup> | | |
|---------|-----------------|-----------------|---------|-----------------|---------|
|         | SARS-CoV-2 positive | Influenza positive | Risk difference (95% CI) | SARS-CoV-2 positive | Influenza positive | Risk difference (95% CI) |
| VTE (diagnoses only) | 17/7920 (0.2) | 11,6682 (0.2) | 0.0 (-0.1 to 0.2) | 23/1540 (1.5) | 147/9599 (1.5) | -0.0 (-0.7 to 0.6) |
| Deep vein thrombosis | 5/7920 (0.1) | NA | - | 7/1540 (0.5) | NA | - |
| Pulmonary embolism | 12/7920 (0.2) | NA | - | 16/1540 (1.0) | NA | - |
| VTE (incl. prescriptions) | 24/7920 (0.3) | NA | - | 36/1540 (2.3) | NA | - |
| Major bleeding | 11/7920 (0.1) | 32,6682 (0.5) | -0.3 (-0.5 to -0.2) | 36/1540 (2.3) | 234/9599 (2.4) | -0.1 (-0.9 to 0.7) |

### VTE in subgroups

#### VTE risk factors

|         | Non-hospitalized | | | Hospitalized<sup>a</sup> | | |
|---------|-----------------|-----------------|---------|-----------------|---------|
|         | SARS-CoV-2 positive | Influenza positive | Risk difference (95% CI) | SARS-CoV-2 positive | Influenza positive | Risk difference (95% CI) |
| No | NA | NA | - | NA | NA | - |
| Yes | NA | NA | - | NA | NA | - |
| Sex | | | | | | |
| Female | NA | 63,696 (0.2) | - | NA | 64,4688 (1.4) | - |
| Male | NA | 52,996 (0.2) | - | NA | 83,4911 (1.7) | - |
| Age | | | | | | |
| 0–64 | 10,6758 (0.1) | 54,723 (0.1) | 0.0 (-0.1 to 0.2) | 11,523 (2.1) | 49,3411 (1.4) | 0.7 (0.6 to 1.9) |
| 65+ | 7,1162 (0.6) | 6,1959 (0.3) | 0.3 (-0.2 to 0.8) | 12,1017 (1.2) | 98,6158 (1.6) | -0.4 (-1.1 to 0.3) |
| Charlson score | | | | | | |
| 0 | NA | NA | - | NA | NA | - |
| ≥1 | NA | NA | - | NA | NA | - |

Abbreviations: CI, confidence interval; incl., including; NA, not applicable as Danish regulations do not allow reporting of less than 5 individuals in each cell; SARS-CoV-2, severe acute respiratory syndrome corona virus 2; VTE, venous thromboembolism.

<sup>a</sup>Numbers refers to start of follow-up. A large number of patients were hospitalized at end of follow-up, 201 SARS-CoV-2 positive patients and 2037 influenza patients.

<sup>b</sup>Among hospitalized SARS-CoV-2 patients, VTE was diagnosed in 16/991 from February 27 through March 31 and in 7/549 from April 1 through April 31, 2020.
Since most previous studies of VTE in SARS-CoV-2 infection lack comparison cohorts, it remains unclear if risk exceeds that of other infections or medical conditions [24–26]. Danish registry-based studies on bacteremia observed absolute VTE risks comparable to estimates in the present study [27, 28], whereas others have found a VTE incidence of 37% in 113 ICU patients with severe sepsis despite universal use of guideline-recommended thromboprophylaxis [29]. However, most sepsis patients in that study had DVT, and PE was only found in 4%.

SARS-CoV-2 may induce thrombosis by immobilization and hospitalization [11]. More directly, the virus may also cause endothelial dysfunction by cell invasion and has been found to invoke hyperinflammation, anti-phospholipid antibody production, and coagulopathy [2]. Some authors suggest that formation of local pulmonary diseases; DOAC, direct oral anticoagulant; LMWH, low-molecular weight heparin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VTE, venous thromboembolism.

Some patients changed anticoagulant therapy during admission, and some received simultaneous therapy with two anticoagulants.
<table>
<thead>
<tr>
<th>Observations</th>
<th>Total</th>
<th>Non-ICU</th>
<th>ICU</th>
<th>Anticoagulant therapy</th>
<th>No anticoagulant therapy</th>
<th>Anticoagulant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE during admission or follow-up, n (% of n)</td>
<td>28 (5)</td>
<td>4 (3)</td>
<td>15 (5)</td>
<td>9b (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>24 (4)</td>
<td>4 (3)</td>
<td>11c (4)</td>
<td>9b (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>6d (1)</td>
<td>0</td>
<td>4 (1)</td>
<td>2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding during admission, n (% of n)</td>
<td>17 (3)</td>
<td>2e (1)</td>
<td>0</td>
<td>15e (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS, retroperitoneal or intraocular hemorrhage</td>
<td>3 (1)</td>
<td>0</td>
<td>0</td>
<td>3 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion &gt;1 unit of blood or significant intervention required</td>
<td>13 (2)</td>
<td>2 (1)</td>
<td>0</td>
<td>11 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage as a contributing factor to death</td>
<td>3 (1)</td>
<td>0</td>
<td>0</td>
<td>3 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality, n (% of n)</td>
<td>124 (20)</td>
<td>31 (22)</td>
<td>42 (13)</td>
<td>48 (36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with VTE before death</td>
<td>4 (1)</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with major bleeding during admission before death</td>
<td>7 (1)</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: VTE, venous thromboembolism; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CNS, central nervous system; DOAC, direct oral anticoagulant; ICU, intensive care unit; LMWH, low-molecular weight heparin.

aAnticoagulant therapy consisted of standard dose LMWH in 90 patients, intermediate/high dose LMWH in 27 patients, DOACs in 14 patients, and vitamin K antagonist in 1 patient.
bThree patients not receiving anticoagulant treatment were diagnosed with pulmonary embolism before they were transferred to the intensive care unit and anticoagulant treatment started.
cPre-existing risk factors before diagnosis of VTE were present in 4 patients (ie, airplane travel within 30 days, active cancer treatment within 6 months combined with recent surgery within 30 days, hip surgery within 30 days, and previous deep vein thrombosis in 1 each).
dFor the 2 non-ICU patients with major bleeding, anticoagulant therapy consisted of standard dose LMWH in both patients. For the 15 ICU patients with major bleeding, anticoagulant therapy consisted of standard dose LMWH in 8 patients, intermediate/high-dose LMWH in 5 patients, and DOACs in 2 patients.
Thus far, autopsy studies of deceased SARS-CoV-2 patients have yielded varying results ranging from no VTEs [30, 32] to findings of DVT in 58% (7/12) and PE in 33% (4/12) of patients [33]. This is consistent with older autopsy studies on more than 5000 patients where PE were frequent and found in up to 70% of patients who died from infection, primarily pneumonia and sepsis [34, 35].

Several guidelines and position papers recommend thromboprophylaxis for all hospitalized COVID-19 patients and some even suggest increased dose thromboprophylaxis and extended anticoagulation for up to 45 days postdischarge in selected COVID-19 patients [36–38]. Still, intermediate or therapeutic dose anticoagulation has had little impact on risk of VTE or mortality in previous studies of COVID-19 and was associated with major bleeding events in the current study [4–6, 8, 9, 39–41]. Thus, the present evidence base for aggressive thromboprophylaxis in COVID-19 patients is uncertain and risk-benefit of high dose heparin therapy should be considered while data from ongoing clinical trials are awaited [42, 43].

This study has limitations. Surveillance bias of VTE may be present because diagnostic imaging can be difficult to perform in isolated and mechanically ventilated ICU patients, or patients may have died with undiagnosed VTE. This would result in an underestimation of absolute VTE risk in both severely ill SARS-CoV-2 and influenza patients, but it is unlikely to substantially affect the relative comparison of incidence in these patient groups. On the other hand, since VTE occurrence in SARS-CoV-2 patients received massive attention towards the end of the study period, this may have prompted an increased diagnosis of PEs compared with SARS-CoV-2 negative and influenza patients. Although we were able to include all 9460 SARS-CoV-2 test positive patients in Denmark until May 1, 2020, the national test strategy in this phase was directed at those who were most sick and in need of medical care. A serological survey indicated that 1.1% (n ~ 63 400) of Danish residents had been infected by May 2020 (municipality screening available at www.ssi.dk). Thus, our results are most generalizable to persons with clinically confirmed SARS-CoV-2 infection. Furthermore, missed infections occurring before or after a negative PCR test in test-negative individuals may have diluted any risk differences between test-positive and test-negative individuals. Changes in test strategy during the study period may have resulted in inclusion of less ill and comorbid SARS-CoV-2 positive and negative patients, whereby proportions experiencing the primary outcome would likely decrease. Still, absolute risks of VTE were consistently low among hospitalized SARS-CoV-2 positive individuals. Although the positive predictive value (PPV) of VTE codes in the National Patient Registry are 86–90% for first-time events [44], the sensitivity for VTE in hospitalized SARS-CoV-2 positive patients and hospitalized comparison cohorts may be more moderate as suggested by the higher rates observed by EMR review. Another limitation was lack of information on thromboprophylaxis and in-hospital therapy in registry-based analyses. However, EMR review suggested that use of thromboprophylaxis was very frequent in ICU patients (100%), but rather limited in non-ICU patients in Denmark (31%) compared with other settings.

In this Danish population-based cohort, SARS-CoV-2 was associated with low risk for VTE among nonhospitalized patients and a moderate risk among hospitalized patients. Importantly, VTE risk was not substantially increased compared with hospitalized SARS-CoV-2 test-negative and influenza patients. Diagnosis of major bleeding in nonhospitalized and hospitalized SARS-CoV-2 patients mirrored that of VTE.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. M. D. P. and J. B. conceived the study. M. D. P., J. B., R. W. T., A. P., N. B. J., M. H., L. C. L., and H. N. designed the study. L. C. L. did the registry-based analyses. Medical record review was conducted by J. B., R. W., T. M., O. S., S. L. N., L. F. L., S. B. I., and L. H. O. and was analyzed by J. B. M. D. P. wrote the first draft, which has been critically revised and approved by all authors.

Acknowledgments. The authors thank the Danish Medicines Agency for facilitating the conduct of this study. According to Danish law, data cannot be shared directly by the authors. Data are accessible to authorized researchers after application to the Danish Health Data Authority.

Potential conflicts of interest. T. B. L. reports personal fees/consulting fees from Boehringer Ingelheim, Bayer, MSD and BMS/Pfizer, during the conduct of the study. A. P. reports grants from Alcon, grants from Almirall, grants from Astellas, grants from Astra-Zeneca, grants from BoehringerIngelheim, grants from Novo Nordisk, grants from Servier, and grants from LEO Pharma, outside the submitted work. R. T. reports that The Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. L. C. L. reports participation in research projects funded by Menarini Pharmaceuticals and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the current study. All other authors declare no conflicts of interests. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

Venous Thromboembolism in COVID-19


