Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL COMMENT

Thromboembolism and the Pandemic*

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Severe acute respiratory syndrome- coronavirus-19 with coronavirus disease-2019 (COVID-19) has been associated with thrombotic complications involving both venous and arterial circulations. Severe infections carry a unique laboratory signature including lymphopenia and thrombocytopenia with elevated fibrinogen and fibrin D-dimer, prompting the newly coined term "sepsis-induced coagulopathy" as distinct from disseminated intravascular coagulation. Thrombotic outcomes include an increased incidence of venous thromboembolism (VTE), particularly in the intensive care unit (ICU) setting. Early reports, often published as pre-peer-reviewed letters, warned of high rates of VTE, myocardial infarctions, and strokes often occurring despite prophylaxis and sometimes despite therapeutic anticoagulation. These reports left the medical community bewildered with many entertaining therapeutic anticoagulation for hospitalized patients regardless of their thrombus status. Guideline statements have advocated for aggressive VTE prophylaxis with low-molecular-weight heparin for all hospitalized patients in the absence of contraindications (1-3). For high-risk patients, extended outpatient VTE prophylaxis has been recommended by some but not all investigators (2). Much of this guidance has been based on early reports that have been limited by small sample sizes, heterogeneous patient populations, variable thromboprophylaxis delivery, and varied approaches to outcome determination (mandatory screening vs. clinically driven imaging). In summary, there has been a paucity of robust datasets regarding the thrombotic epidemiology of the COVID-19 pandemic to inform guideline-writing committees.

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In this issue of the *Journal*, Piazza et al. (4) address the epidemiology of thrombotic outcomes among hospitalized and ambulatory patients with laboratory-confirmed COVID-19 infection. Over a 3-week study period beginning in March 2020, 1,114 patients were identified with COVID-19 using a retrospective electronic health record search of a large, integrated health network in the Boston, Massachusetts area. Of these, 399 (35.8%) were hospitalized and 170 (15.3%) required an intensive care stay. Thromboprophylaxis use was high at nearly 90% for ICU patients and 85% for those residing on the clinical ward. Whereas the overall VTE rate among ICU patients was high at 27% (n = 46), the vast majority of these events were attributable to central venous lines (76.9%). Only 4 patients (2.4%) developed a proximal leg deep vein thrombosis (DVT) and 3 patients (1.8%) experienced a pulmonary embolism (PE). There were 13 patients with myocardial infarction, all were non-ST-segment elevation myocardial infarction and none were treated with percutaneous coronary intervention. The percentage of these with type II demand ischemia was not provided. One patient suffered a stroke. For the 229 patients residing on the medical wards, there were no symptomatic leg DVTs and 5 PEs (2.2%), 1 ST-segment elevation myocardial infarction, and no strokes. Of the 715 ambulatory patients, there were no arterial or venous events. Of the entire cohort, there were no major bleeding events reported.

These data provide important real-world arterial and venous thrombotic event rates across a large, integrated health care network and an experienced roster of clinician-scientists devoted to thrombosis research. Whether to interpret these results as

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TABLE 1 Comparative Thromboembolic Rates From Pre-COVID-19 Publications

First Author (Ref. #)	n	Prophylaxis	Proximal Leg DVT	PE	CVC DVT	MI	Stroke	Major Bleed
ICU patients*								
Piazza et al. (4)	170	LMWH	2.3	1.8	17.6	7.7	0.6	NP
PROTECT (6)	3,764	LMWH UFH	5.1 5.8	1.3 2.1	2.3 2.1	NP	NP	5.5 5.6
Cook et al. (7)	261	UFH/LMWH	9.6	1.5	1.5	NP	NP	NP
Lamontagne et al. (8)	3,746	LMWH UFH	2.0	2.1	1.8	NP	NP	NP
Zhang et al. (9)	281	LMWH UFH	3.9	0.4	NP	NP	NP	NP
Kaplan et al. (10)	113	LMWH UFH	11.5	3.5	14.2	NP	NP	NP
Ward patients*								
Piazza et al. (4)	229	LMWH	0.0	2.2	0.0	0.5	0.0	NP
ADOPT (11)	6,758	Apixaban LMWH	2.4 2.5	0.22 0.24	NP	NP	NP	0.47 0.19
MAGELLAN (12)	8,101	Rivaroxaban LMWH	3.9 4.9	0.3 0.5	NP	NP	NP	0.6 0.3
APEX (13)	12,024	Betrixaban LMWH	4.7 6.2	0.3 0.6	NP	NP	0.6 1.1	0.7 0.6

Values are %. *Rates compared with those reported by Piazza et al. (4).

ADOPT = Study of Apixaban for the Prevention of Thrombosis-Related Events in Patients With Acute Medical Illness; APEX = Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study; CVC = central venous catheter; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; MAGELLAN = Venous Thromboembolic Event (VTE) Prophylaxis in Medically Ill Patients; MI = myocardial infarction; NP = not provided; PE = pulmonary embolism; UFH = unfractionated heparin.

alarming or reassuring requires a comparison of expected thromboembolic event rates separate from the pandemic. Apart from the central line-associated venous thrombosis, these event rates do not appear inflated relative to prior published incidence rates from the pre-COVID-19 era. As such, Roberts et al. (5) found that post-hospital discharge-associated VTE rates for COVID-19 patients (4.8 per 1,000 hospital discharges) did not differ compared with 2019 pre-COVID-19 rates (3.1 per 1,000 hospital discharges; odds ratio: 1.6; 95% confidence interval: 0.77 to 3.1; $p = 0.20$). The PROTECT trial (6), published in 2011, compared prophylaxis with low-molecular-weight heparin to unfractionated heparin in 3,764 ICU patients. Enrolled subjects underwent protocolized twice-weekly ultrasound evaluation to maximize DVT capture. Relevant to the current topic, 45% of the recruited patients were admitted for a respiratory illness. Proximal leg DVT was identified in 5.1% and 5.8% whereas PE rates were 1.3% and 2.3% for patients receiving dalteparin and unfractionated heparin, respectively. Additional pre-COVID-19 estimates of VTE rates from hospitalized patients in the ICU and ward setting have comparable frequencies (**Table 1**) (5–13). It would therefore appear that VTE rates reported in the current study are similar to expected rates for patients hospitalized without COVID-19.

There are several important messages to be gleaned from this combined work. First, early reports in the pandemic must be interpreted in the appropriate context. Whereas it is true that rare patients may experience profound thrombotic events as a consequence of this infection, the overall event rates appear to be similar in patients requiring hospital and ICU care apart from the pandemic. It is therefore important to resist the urge to overprevent or overtreat patients and expose them to the serious risks of major bleeding. Adding major hemorrhage to the condition of a patient already severely compromised from the viral infection will undoubtedly increase the mortality risk. Second, clinical guidelines for DVT prophylaxis have been based on decades of rigorous research and provide a sound scaffold for strategies to care for patients with this infection. The systematized approach to delivery of guideline-driven VTE prophylaxis across this large, integrated health network likely contributed to the relatively low rates of serious thrombotic outcomes reported. Third, careful review of the Kaplan-Meier curves for VTE events are informative. VTE events occurred after the first 5 to 7 days following hospital admission and the majority were related to central venous lines in ICU patients. This underscores the importance of a bundled care approach to central venous line management with daily assessment of the continued necessity of the

central access. Whereas central venous lines are convenient, the potential for thrombotic or infectious complications requires prompt removal when no longer absolutely needed. Fourth, few reports have provided bleeding complication rates for COVID-19 patients. Two groups have reported rates between 0% and 2.7% (14,15). Without these data, it is difficult to provide a balanced recommendation regarding anticoagulant use in this setting.

In summary, the paper by Piazza et al. (4) adds important information to the growing number of publications of COVID-19-associated thromboembolism. A number of important clinical trials aimed at optimizing thrombo-prophylaxis during hospitalization, following hospital dismissal, and in ambulatory settings are underway. Until available, the lessons of thoughtful anticoagulant prophylaxis and treatment guidelines harvested from years of clinical research appear to apply.

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