Clinical Epidemiology

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ORIGINAL RESEARCH

Risk of Arterial and Venous Thrombotic Events Among Patients with COVID-19: A Multi-National Collaboration of Regulatory Agencies from Canada, Europe, and United States

Vincent Lo Re III[1,2,*], Noelle M Cocoros[3,4,*], Rebecca A Hubbard[2], Sarah K Dutcher[5], Craig W Newcomb[2], John G Connolly[3,4], Silvia Perez-Vilar[5], Dena M Carbonari[2], Maria E Kempner[3,4], José J Hernández-Muñoz[5], Andrew B Petrone[3,4], Allyson M Pishko[6], Meighan E Rogers Driscoll[3,4], James T Brash[7], Sean Burnett[8,9], Catherine Cohet[10], Matthew Dahl[8,11], Terese A DeFor[12], Antonella Delmestri[13], Djeneba Audrey Djibo[14], Talita Duarte-Salles[15,16], Laura B Harrington[17], Melissa Kampman[18], Jennifer L Kuntz[19], Xavier Kurz[10], Núria Mercadé-Besora[15], Pamala A Pawloski[12], Peter R Rijnbeek[16], Sarah Seager[7], Claudia A Steiner[20,21], Katia Verhamme[16], Fangyun Wu[8,22], Yunping Zhou[23], Edward Burn[13], J Michael Paterson[8,22,*], Daniel Prieto-Alhambra[13,16,*]

[1]Division of Infectious Diseases, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Population Medicine, Harvard Medical School, Boston, MA, USA; [4]Harvard Pilgrim Healthcare Institute, Boston, MA, USA; [5]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA; [6]Division of Hematology and Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [7]IQVIA, Real World Solutions, Brighton, UK; [8]Canadian Network for Observational Drug Effect Studies (CNODES), Toronto, Ontario, Canada; [9]Therapeutics Initiative, University of British Columbia, Vancouver, British Columbia, Canada; [10]Data Analytics and Methods Task Force, European Medicines Agency, Amsterdam, Netherlands; [11]Manitoba Centre for Health Policy, University of Manitoba, Winnipeg, Manitoba, Canada; [12]HealthPartners Institute, Bloomington, MN, USA; [13]Pharmaco- and Device Epidemiology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK; [14]CVS Health, Blue Bell, PA, USA; [15]Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain; [16]Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [17]Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA; [18]Health Canada, Ottawa, Ontario, Canada; [19]Kaiser Permanente Northwest Center for Health Research, Portland, OR, USA; [20]Kaiser Permanente Colorado Institute for Health Research, Aurora, CO, USA; [21]Colorado Permanente Medical Group, Denver, CO, USA; [22]ICES, Toronto, Ontario, Canada; [23]Humana Healthcare Research, Inc., Louisville, KY, USA

*These authors contributed equally to this work

Correspondence: Vincent Lo Re III, Division of Infectious Diseases, Department of Medicine, Division of Epidemiology, Department of Biostatistics, Epidemiology, and Informatics, Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, 836 Blockley Hall, 423 Guardian Drive, Philadelphia, PA, 19104-6021, USA, Fax +1 215 573 5315, Email vincentl@pennmedicine.upenn.edu

Purpose: Few studies have examined how the absolute risk of thromboembolism with COVID-19 has evolved over time across different countries. Researchers from the European Medicines Agency, Health Canada, and the United States (US) Food and Drug Administration established a collaboration to evaluate the absolute risk of arterial (ATE) and venous thromboembolism (VTE) in the 90 days after diagnosis of COVID-19 in the ambulatory (eg, outpatient, emergency department, nursing facility) setting from seven countries across North America (Canada, US) and Europe (England, Germany, Italy, Netherlands, and Spain) within periods before and during COVID-19 vaccine availability.

Patients and Methods: We conducted cohort studies of patients initially diagnosed with COVID-19 in the ambulatory setting from the seven specified countries. Patients were followed for 90 days after COVID-19 diagnosis. The primary outcomes were ATE and VTE over 90 days from diagnosis date. We measured country-level estimates of 90-day absolute risk (with 95% confidence intervals) of ATE and VTE.

Received: 9 November 2023
Accepted: 23 January 2024
Published: 10 February 2024

Results: The seven cohorts included 1,061,565 patients initially diagnosed with COVID-19 in the ambulatory setting before COVID-19 vaccines were available (through November 2020). The 90-day absolute risk of ATE during this period ranged from 0.11% (0.09–0.13%) in Canada to 1.01% (0.97–1.05%) in the US, and the 90-day absolute risk of VTE ranged from 0.23% (0.21–0.26%) in Canada to 0.84% (0.80–0.89%) in England. The seven cohorts included 3,544,062 patients with COVID-19 during vaccine availability (beginning December 2020). The 90-day absolute risk of ATE during this period ranged from 0.06% (0.06–0.07%) in England to 1.04% (1.01–1.06%) in the US, and the 90-day absolute risk of VTE ranged from 0.25% (0.24–0.26%) in England to 1.02% (0.99–1.04%) in the US.

Conclusion: There was heterogeneity by country in 90-day absolute risk of ATE and VTE after ambulatory COVID-19 diagnosis both before and during COVID-19 vaccine availability.

Plain Language Summary: Cohort studies of patients diagnosed with COVID-19 in both the ambulatory and hospital settings have suggested that SARS-CoV-2 infection promotes hypercoagulability that could lead to arterial or venous thromboembolism. However, few studies have examined how the risk of thromboembolism with COVID-19 has evolved over time across different countries. A new collaboration was established among the regulatory authorities of Canada, Europe, and the US within the International Coalition of Medicines Regulatory Authorities to evaluate the 90-day risk of both arterial and venous thromboembolism after initial diagnosis of COVID-19 in the ambulatory or hospital setting from seven countries across North America (Canada, US) and Europe (England, Germany, Italy, Netherlands, and Spain) within periods before and during COVID-19 vaccine availability. The study found that there was variability in the risk of both arterial and venous thromboembolism by month across the countries among patients initially diagnosed with COVID-19 in the ambulatory or hospital setting. Differences in the healthcare systems, prevalence of comorbidities in the study cohorts, and approaches to the case definitions of thromboembolism likely contributed to the variability in estimates of thromboembolism risk across the countries.

Keywords: COVID-19, ischemic stroke, myocardial infarction, thromboembolism, venous thromboembolism

Introduction

SARS-CoV-2 infection can induce a hypercoagulable state that promotes arterial thromboembolism (ATE) or venous thromboembolism (VTE).[1–5] Observational studies examining thrombotic complications from COVID-19 have generally evaluated events from early in the pandemic within specific geographic regions.[6,7] However, few studies have examined how the absolute risk of thromboembolism has evolved over time with different SARS-CoV-2 variants and in the era of COVID-19 vaccination, and fewer still have compared these across different countries. Consequently, major knowledge gaps remain regarding the incidence of arterial and venous thrombotic complications with COVID-19 across different countries. Studies that evaluate the epidemiology of thromboembolism using real-world data provide important estimates of their frequency, which can inform the need for and development of interventions to reduce the risk of these serious adverse outcomes.

In response to the COVID-19 pandemic, the International Coalition of Medicines Regulatory Authorities committed to cooperate on observational studies of COVID-19 to generate real-world evidence.[8] Researchers from the European Medicines Agency (EMA), Health Canada, and the United States (US) Food and Drug Administration (FDA) established a collaboration to evaluate the risk of thromboembolism among patients with COVID-19 using real-world data from seven countries across North America (Canada, US) and Europe (England, Germany, Italy, Netherlands, and Spain). The main objective was to evaluate the absolute risk of ATE and VTE (separately) in the 90 days after diagnosis of COVID-19 in the ambulatory (ie, outpatient, emergency department, or institutional [eg, skilled nursing facility, long-term care facility]) and hospital setting within periods before and during COVID-19 vaccine availability.

Material and Methods

Study Design and Data Sources

We evaluated data from a series of retrospective cohort studies among patients diagnosed with COVID-19 within routinely collected healthcare data from: 1) three Canadian provinces (British Columbia, Manitoba, and Ontario) within the Canadian Network for Observational Drug Effects Studies (CNODES);[9] 2) England (Clinical Practice Research Datalink [CPRD] Aurum);[10] 3) Germany (IQVIA Disease Analyzer Germany);[11] 4) Italy (IQVIA Longitudinal Patient Data Italy);[12]

5) Netherlands (Integrated Primary Care Information [IPCI]);[13] 6) Spain (Information System for Research in Primary Care [SIDIAP];[14] and 7) two US national health insurers (Aetna; Humana, Inc.) and four US regional integrated delivery systems (HealthPartners; Kaiser Permanente Colorado; Kaiser Permanente Northwest; Kaiser Permanente Washington) within the FDA Sentinel System[15] (see Table 1 for details on country-specific data and observation periods).

The Canadian data were population-based and included demographics, medical diagnoses (recorded using International Classification of Diseases, Ninth and Tenth Revision, Canadian Modification [ICD-9-CA, ICD-10-CA] codes), procedures, laboratory results, and dispensed outpatient medications transformed into the Sentinel Common Data Model.[9] The same analytic program, developed and implemented within the FDA Sentinel System, was run for the Canadian data. The research protocol was reviewed and approved by Health Canada and by each participating CNODES provincial data center. In British Columbia and Manitoba, regulatory approvals were obtained from University of British Columbia Clinical Research Ethics Board and the University of Manitoba Health Research Ethics Board, respectively. Research ethics board approval was not legally required in Ontario as ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act (PHIPA), which authorizes it to collect and use personal health information without consent for the purposes of health service/system evaluation, planning, monitoring, and improvement. Use of the data in this project was authorized under section 45 of PHIPA and approved by ICES' Privacy and Legal Office.

Data from the five participating European countries were mapped to the Observational Medical Outcomes Partnership Common Data Model and analyzed in a distributed manner with common analytic code run by each site and aggregated results returned without transferring patient-level data between sites.[16] Data from IQVIA Disease Analyzer Germany were collected from extracts of patient management software used by general practitioners (GPs) and specialists practicing in ambulatory

Table 1 Overview of Data Sources Used for This Study

Database Requirement	CNODES (Canada)[a]	Clinical Practice Research Datalink Aurum (England)	IQVIA Disease Analyzer (Germany)	IQVIA Longitudinal Patient Data (Italy)	Integrated Primary Care Information (Netherlands)	Information System for Research in Primary Care (Spain)[b]	FDA Sentinel (United States)[c]
Type of healthcare data	Hospital/ED Discharge Abstracts and Claims	Electronic Medical Record	Electronic Medical Record	Electronic Medical Record	Electronic Medical Record	Electronic Medical Record	Electronic Medical Record and Claims
Diagnostic coding scheme[d]	ICD-9-CA, ICD-10-CA	SNOMED	ICD-10-GM	ICD-9	ICPC	ICD-10-CM	ICD-10-CM
Data source details regarding care setting	All care settings available	Primarily ambulatory, includes GP-recorded hospital diagnoses	Primarily ambulatory	Primarily ambulatory, includes GP-recorded hospital diagnoses	Primarily ambulatory, includes GP-recorded hospital diagnoses	Primary ambulatory, linked hospital diagnoses	All care settings available
Pharmacy data	Dispensed Medications	Prescriptions	Prescriptions	Prescriptions	Prescriptions	Prescriptions, Dispensed Medications	Dispensed Medications
Laboratory data available	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date of death available	Yes	Yes	Yes (Incomplete)	Yes	Yes	Yes	Yes

(*Continued*)

Table 1 (Continued).

Database Requirement	CNODES (Canada)[a]	Clinical Practice Research Datalink Aurum (England)	IQVIA Disease Analyzer (Germany)	IQVIA Longitudinal Patient Data (Italy)	Integrated Primary Care Information (Netherlands)	Information System for Research in Primary Care (Spain)[b]	FDA Sentinel (United States)[c]
Pre-vaccine availability period:							
COVID-19 identification	April 2020 – Nov 2020	March 2020 – Nov 2020	March 2020 – Nov 2020	March 2020 – Nov 2020	March 2020 – Nov 2020	March 2020 – Nov 2020	April 2020 – Nov 2020
ATE/VTE outcome identification[e]	April 2020 – Feb 2021	April 2020 – Nov 2020	April 2020 – Nov 2020	April 2020 – Nov 2020	April 2020 – Nov 2020	April 2020 – Nov 2020	April 2020 – Feb 2021
Mortality outcome identification[f]	April 2020 – Mar 2021	April 2020 – Nov 2020	April 2020 – Nov 2020	April 2020 – Nov 2020	April 2020 – Nov 2020	April 2020 – Nov 2020	April 2020 – Mar 2021
Post-vaccine availability period:							
COVID-19 identification	Dec 2020 – Dec 2021	Dec 2020 – Jan 2022	Dec 2020 – Sept 2022	Dec 2020 – Sept 2022	Dec 2020 – Dec 2021	Dec 2020 – June 2021	Dec 2020 – Dec 2021
ATE/VTE outcome identification[e]	Dec 2020 – March 2022	Dec 2020 – Jan 2022	Dec 2020 – Sept 2022	Dec 2020 – Oct 2022	Dec 2020 – Dec 2021	Dec 2020 – June 2021	Dec 2020 – March 2022
Mortality outcome identification[f]	Dec 2020 – April 2022	Dec 2020 – Jan 2022	Dec 2020 – Sept 2022	Dec 2020 – Oct 2022	Dec 2020 – Dec 2021	Dec 2020 – June 2021	Dec 2020 – April 2022

Notes: [a]Included data from British Columbia, Manitoba, and Ontario; the post-vaccine availability period included data from only British Columbia and Ontario. [b]Included data from Catalonia, Spain. [c]Included data from two national health insurers (Aetna; Humana, Inc.) and four regional integrated delivery systems (HealthPartners; Kaiser Permanente Colorado; Kaiser Permanente Northwest; Kaiser Permanente Washington); the post-vaccine availability period did not include Kaiser Permanente Washington. [d]The data within the European Union countries used for these analyses were mapped to the Observational Medical Outcomes Partnership (OMOP) data model, which utilizes SNOMED. [e]ATE and VTE outcomes were identified within 90 days of COVID-19 diagnosis. [f]Mortality was assessed within 30 days of an ATE or VTE event.
Abbreviations: ATE, arterial thromboembolism; CNODES, Canadian Network for Observational Drug Effects Studies; ED, emergency department; FDA, Food and Drug Administration; GP, general practitioner; ICD-9, International Classification of Diseases, Ninth Revision; ICD-9-CA, International Classification of Diseases, Ninth Revision, Canadian Modification; ICD-10-CA, International Classification of Diseases, Tenth Revision, Canadian Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; ICD-10-GM, International Classification of Diseases, Tenth Revision, German Modification; ICPC, International Classification of Primary Care; SNOMED, Systemized Nomenclature of Medicine; VTE, venous thromboembolism.

care settings.[11] IQVIA Longitudinal Patient Data Italy included anonymized patient records collected from software used by GPs.[12] The IPCI database was comprised of primary care electronic medical records (EMR) of patients registered with GPs throughout the Netherlands.[13] The CPRD Aurum database contained primary care data contributed by GPs predominantly from England (with a small portion from Northern Ireland).[10] Data from SIDIAP, a primary care records database from Catalonia, Spain, was linked to the minimum basic set of hospital discharge data, which included diagnoses and procedures recorded during hospitalizations.[17] Within these countries, GPs serve as gatekeepers to the healthcare systems and provide centralized care in the community. Across all European data sources, demographic data, comorbidities (identified by Systematized Nomenclature of Medicine [SNOMED] clinical terms), and outpatient prescriptions were available. The protocol for this research was reviewed by the EMA, and data stewards from Spain, the Netherlands, and England obtained ethics/permissions for use of data from these countries. Use of data from IQVIA did not require regulatory approval.

Data within the US were from the FDA Sentinel System, a multi-site distributed data network with standardized, quality-checked claims and EMR data.[15] The six data partners included were selected because of their ability to update their data frequently for COVID-19 response.[18] Available data included health plan enrollment dates, demographics, diagnoses

(recorded using International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] codes), procedures, laboratory results, and dispensed outpatient medications, which were transformed into the Sentinel Common Data Model.[9] This Sentinel project was a public health surveillance activity conducted under FDA authority and was not subject to Institutional Review Board oversight.[19,20]

Study Patients

Patients with COVID-19 were included if they: 1) had an initial COVID-19 diagnosis or positive SARS-CoV-2 nucleic acid test from any care setting recorded between April 1, 2020 and database-specific end dates (see Table 1); 2) were ≥18 years of age at COVID-19 diagnosis or positive laboratory test; and 3) prior to COVID-19 identification, had health care/insurance coverage for ≥365 days in the European or US data and ≥730 days in the Canadian provincial data (to permit a longer lookback for comorbidity assessment due to the fewer number of diagnosis codes permissible on Canadian physician service claims). The primary analytic cohort encompassed patients with COVID-19 who were initially identified via diagnosis or positive nucleic acid test in the ambulatory (ie, outpatient, emergency department, or institutional) setting. Patients initially diagnosed with COVID-19 in the hospital in Canada, Spain, and the US, the only sites where hospital data were readily available, were included in a secondary analytic cohort.

Since COVID-19 vaccination might affect the risk of thrombosis after SARS-CoV-2 infection,[21] we created separate cohorts of patients with COVID-19 identified during a period prior to COVID-19 vaccine availability (April 1, 2020–November 30, 2020) and during a period when these vaccines were available (beginning December 1, 2020; Table 1).[7,22] COVID-19 vaccination may have occurred in the community or workplace, outside of healthcare settings and without reimbursement by health insurers. As a result, documentation of immunization may not be complete in administrative claims or EMR databases.[23,24] Consequently, we evaluated periods of COVID-19 stratified by availability of COVID-19 vaccination.

Within each cohort, we defined the index date as the earliest date of diagnosis or positive laboratory test for COVID-19 during the corresponding study period. We excluded patients with diagnostic or laboratory evidence of COVID-19 within 90 days prior to the index date to ensure inclusion of incident infections. Canadian and US patients diagnosed with another respiratory virus (ie, adenovirus, enterovirus, human metapneumovirus, influenza, parainfluenza, respiratory syncytial virus, rhinovirus) in hospital records or outpatient claims within ±14 days of their COVID-19 index date were also excluded to isolate the effect of SARS-CoV-2 on risk of thrombotic outcomes. Patients could be included in cohorts both prior to and during COVID-19 vaccine availability, since reinfection occurs, but only the first SARS-CoV-2 infection in each period was included. Follow-up continued until a study endpoint (defined below), disenrollment from medical or pharmacy coverage (relevant to US data), migration (relevant to non-US data), death, or 90 days after index date, whichever occurred first.

Main Study Outcomes

We separately evaluated two primary study endpoints: 1) ATE, defined by diagnosis of acute myocardial infarction or ischemic stroke and 2) VTE, defined by diagnosis of acute deep venous thrombosis (DVT) or pulmonary embolism (PE).[7,22] Within the Canadian and US data, acute myocardial infarction, ischemic stroke, and PE were defined by principal or contributory hospital discharge diagnoses; DVT was defined by principal or contributory hospital discharge diagnosis or emergency department diagnosis, since patients with an acute DVT may be diagnosed in an emergency department and treated without hospitalization. We employed several approaches to ascertain thrombotic events and minimize outcome misclassification. For the North American countries, events were ascertained using ICD-9-CA and ICD-10-CA (Canada) or ICD-10-CM (US) diagnoses, as previously defined,[7] mapped from International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnoses for ATE[25–28] and VTE[29,30] that were previously validated against medical record review. For the European countries, events were ascertained using ICD-9 (Italy), ICD-10-CM (Spain), ICD-10-GM (Germany), International Classification of Primary Care (Netherlands), and SNOMED (England) diagnostic codes recorded by the patient's GP (England, Italy, Netherlands, Spain), outpatient specialist (Germany), or hospital discharge diagnosis (Spain). GPs and outpatient specialists record diagnoses from hospital events. Code lists used for outcome ascertainment in the European data have been previously reported.[6]

As a secondary endpoint, we examined all-cause mortality within 30 days after an ATE or VTE event. Death was identified in all databases except for Germany, from which it is not reliably captured.

Covariates

Data included setting of COVID-19 diagnosis (ambulatory versus inpatient), age at diagnosis, sex, month of diagnosis, number of hospital encounters in the 365 days before diagnosis, and number of ambulatory encounters (visits to ambulatory/urgent sites for medical care, laboratory tests, or other procedures) in the 365 days before diagnosis.

During the specified baseline period of each country's data, we identified diagnoses recorded within hospital and ambulatory records that might affect risk of ATE or VTE, including atrial fibrillation/flutter, cancer, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, prior cardiovascular disease (defined by myocardial infarction, cerebrovascular disease, coronary artery disease, peripheral artery disease, or acute limb ischemia), prior VTE (defined by DVT, PE, or other venous thrombosis), hypertension, hyperlipidemia, neurological diseases that promote immobility (defined by Alzheimer's disease, amyotrophic lateral sclerosis, dementia, Guillain-Barré syndrome, multiple sclerosis, muscular dystrophy, Parkinson's disease), and rheumatologic disease.

Statistical Analysis

Among patients initially diagnosed with COVID-19 in the ambulatory setting, we measured country-level estimates of the unadjusted 90-day absolute risk (with 95% confidence intervals [CIs]) of ATE and VTE, defined as number of events ascertained within 90 days after the index date, overall and stratified by age (18–44; 45–54; 55–64; 65–74; 75–84; ≥85 years), sex, and month of diagnosis during the pre- and post-vaccine periods. The analysis was repeated among patients initially diagnosed with COVID-19 in the hospital from Canada, Spain, and the US. Among patients with a thrombotic event, we determined the absolute risk of death within the 30 days (including event date) following ATE or VTE. Complete data were available for all variables evaluated in these analyses; there were no missing data for variables of interest. Data were analyzed using SAS (SAS Institute Inc., Cary, North Carolina, USA) for US and Canadian data and R with RStudio for European data.

Results

90-Day Risk of ATE and VTE with Ambulatory-Diagnosed COVID-19

Across the seven participating countries, we identified 1,061,565 eligible patients initially diagnosed with COVID-19 in the ambulatory setting before COVID-19 vaccines were available and 3,544,062 eligible patients initially diagnosed with COVID-19 in the ambulatory setting during vaccine availability (Table 2). In both periods of COVID-19 vaccine availability and across all countries, the majority of ambulatory-diagnosed persons were female, and 18–44 was the most common age group (Table 2). Ambulatory-diagnosed patients were predominantly included during October–November 2020 in the pre-COVID-19 vaccine period and during November 2021-March 2022 after COVID-19 vaccines became available. The prevalence of baseline diagnoses that might affect risk of ATE or VTE differed by country (Table 2). For example, the prevalence of hypertension ranged from 11.5% in England to 46.8% in the US, prevalence of diabetes ranged from 6.2% in England to 22.5% in the US, and prevalence of cancer ranged from 3.9% in England to 16.3% in Canada.

The 90-day absolute risk of ATE and VTE after ambulatory-diagnosed COVID-19 varied across the countries before and during vaccine availability (Table 3). Prior to COVID-19 vaccine availability, the 90-day absolute risk of ATE ranged from 0.11% (95% CI, 0.09–0.13%) in Canada to 1.01% (95% CI, 0.97–1.05%) in the US. During COVID-19 vaccine availability, the 90-day absolute risk of ATE ranged from 0.06% (95% CI, 0.06–0.07%) in England to 1.04% (95% CI, 1.01–1.06%) in the US. Prior to vaccine availability, the 90-day absolute risk of VTE ranged from 0.23% (95% CI, 0.21–0.26%) in Canada to 0.84% (95% CI, 0.80–0.89%) in England. During vaccine availability, the 90-day absolute risk of VTE ranged from 0.25% (95% CI, 0.24–0.26%) in England to 1.02% (95% CI, 0.99–1.04%) in the US. Within each country, the 90-day risk of ATE and VTE was higher for patients who were older and male during both periods (Supplemental Table 1). There was variability in the risk of ATE and VTE observed among patients with ambulatory-diagnosed COVID-19 by month across the countries (Figure 1 and Supplemental Table 2). A decrease in ATE risk was observed in Spain and England in June 2021 and in the US in December 2021.

Table 2 Characteristics of Patients Initially Diagnosed with COVID-19 in the Ambulatory (ie, Outpatient, Emergency Department, or Institutional) Setting Prior to and During COVID-19 Vaccine Availability, by Country

Panel A								
Characteristic[a]	**Canada**[b]		**England**[c]		**Germany**[d]		**Italy**[e]	
	Pre-Vaccine Availability	**Post-Vaccine Availability**	**Pre-Vaccine Availability**	**Post-Vaccine Availability**	**Pre-Vaccine Availability**	**Post-Vaccine Availability**	**Pre-Vaccine Availability**	**Post-Vaccine Availability**
Total patients	124,048	678,907	163,103	1,137,245	130,004	575,160	19,173	87,319
Age (years)								
Mean (SD)	47.4 (19.7)	42.9 (16.9)	50.0 (18.9)	43.0 (16.0)	46.0 (17.5)	47.0 (17.2)	52.0 (18.0)	50.0 (18.0)
18–44 years	61,495 (49.6%)	394,566 (58.1%)	67,980 (41.7%)	641,513 (56.4%)	65,442 (50.3%)	266,399 (46.3%)	6,699 (34.9%)	34,365 (39.4%)
45–54 years	21,569 (17.4%)	118,500 (17.5%)	31,911 (19.6%)	226,979 (20.0%)	24,548 (18.9%)	111,359 (19.4%)	4,155 (21.7%)	18,673 (21.4%)
55–64 years	18,561 (15.0%)	93,412 (13.8%)	27,766 (17.0%)	151,222 (13.3%)	22,319 (17.2%)	113,108 (19.7%)	3,845 (20.1%)	15,627 (17.9%)
65–74 years	8,944 (7.2%)	42,787 (6.3%)	15,686 (9.6%)	67,990 (6.0%)	8,509 (6.5%)	42,948 (7.5%)	2,187 (11.4%)	9,503 (10.9%)
75–84 years	5,998 (4.8%)	18,126 (2.7%)	11,597 (7.1%)	33,627 (3.0%)	6,017 (4.6%)	27,396 (4.8%)	1,470 (7.7%)	6,329 (7.2%)
≥85 years	7,481 (6.0%)	11,516 (1.7%)	8,163 (5.0%)	15,914 (1.4%)	3,169 (2.4%)	13,950 (2.4%)	817 (4.3%)	2,822 (3.2%)
Female sex	65,877 (53.1%)	349,783 (51.5%)	96,212 (59.0%)	610,711 (53.7%)	72,181 (55.5%)	307,877 (53.5%)	10,980 (57.3%)	49,977 (57.2%)
Month of COVID-19 diagnosis								
March 2020	–	–	16,910 (10.4%)	–	10,041 (7.7%)	–	2,052 (10.7%)	–
April 2020	12,845 (10.4%)	–	37,624 (23.1%)	–	11,152 (8.6%)	–	1,459 (7.6%)	–
May 2020	8,099 (6.5%)	–	14,740 (9.0%)	–	8,322 (6.4%)	–	721 (3.8%)	–
June 2020	4,226 (3.4%)	–	7,281 (4.5%)	–	6,805 (5.2%)	–	341 (1.8%)	–
July 2020	3,445 (2.8%)	–	4,565 (2.8%)	–	9,919 (7.6%)	–	179 (0.9%)	–
August 2020	4,443 (3.6%)	–	5,901 (3.6%)	–	11,673 (9.0%)	–	391 (2.0%)	–
September 2020	11,954 (9.6%)	–	14,491 (8.9%)	–	17,274 (13.3%)	–	838 (4.4%)	–
October 2020	25,783 (20.8%)	–	27,699 (17.0%)	–	23,974 (18.4%)	–	4,216 (22.0%)	–
November 2020	53,253 (42.9%)	–	33,892 (20.8%)	–	30,844 (23.7%)	–	8,976 (46.8%)	–

(*Continued*)

https://doi.org/10.2147/CLEP.S448980

Table 2 (Continued).

Panel A								
Characteristic[a]	**Canada[b]**		**England[c]**		**Germany[d]**		**Italy[e]**	
	Pre-Vaccine Availability	**Post-Vaccine Availability**	**Pre-Vaccine Availability**	**Post-Vaccine Availability**	**Pre-Vaccine Availability**	**Post-Vaccine Availability**	**Pre-Vaccine Availability**	**Post-Vaccine Availability**
December 2020	–	65,505 (9.6%)	–	76,212 (6.7%)	–	29,587 (5.1%)	–	4,650 (5.3%)
January 2021	–	68,766 (10.1%)	–	23,678 (2.1%)	–	21,907 (3.8%)	–	3,233 (3.7%)
February 2021	–	31,866 (4.7%)	–	10,126 (0.9%)	–	14,031 (2.4%)	–	3,075 (3.5%)
March 2021	–	52,340 (7.7%)	–	5,908 (0.5%)	–	21,477 (3.7%)	–	5,268 (6.0%)
April 2021	–	102,185 (15.1%)	–	7,706 (0.7%)	–	19,702 (3.4%)	–	2,909 (3.3%)
May 2021	–	48,949 (7.2%)	–	36,870 (3.2%)	–	11,402 (2.0%)	–	1,305 (1.5%)
June 2021	–	9,729 (1.4%)	–	111,457 (9.8%)	–	5,884 (1.0%)	–	470 (0.5%)
July 2021	–	5,198 (0.8%)	–	95,180 (8.4%)	–	5,867 (1.0%)	–	754 (0.9%)
August 2021	–	23,022 (3.4%)	–	75,614 (6.6%)	–	6,775 (1.2%)	–	1,027 (1.2%)
September 2021	–	26,313 (3.9%)	–	41,620 (3.7%)	–	10,636 (1.8%)	–	767 (0.9%)
October 2021	–	19,782 (2.9%)	–	105,790 (9.3%)	–	13,170 (2.3%)	–	646 (0.7%)
November 2021	–	20,640 (3.0%)	–	106,234 (9.3%)	–	35,025 (6.1%)	–	1,555 (1.8%)
December 2021	–	204,612 (30.1%)	–	308,203 (27.1%)	–	24,542 (4.3%)	–	6,299 (7.2%)
January 2022	–	–	–	132,647 (11.7%)	–	44,876 (7.8%)	–	16,696 (19.1%)
February 2022	–	–	–	–	–	57,486 (10.0%)	–	5,378 (6.2%)
March 2022	–	–	–	–	–	82,714 (14.4%)	–	6,897 (7.9%)
April 2022	–	–	–	–	–	40,230 (7.0%)	–	6,230 (7.1%)
May 2022	–	–	–	–	–	21,986 (3.8%)	–	3,637 (4.2%)
June 2022	–	–	–	–	–	29,876 (5.2%)	–	4,614 (5.3%)
July 2022	–	–	–	–	–	38,153 (6.6%)	–	7,603 (8.7%)
August 2022	–	–	–	–	–	20,076 (3.5%)	–	2,716 (3.1%)
September 2022	–	–	–	–	–	19,758 (3.4%)	–	1,590 (1.8%)

Recent Encounters (mean, SD)[f]								
Number of Hospital Encounters	0.1 (0.4)	0.1 (0.3)	–	–	–	–	–	–
Number of Ambulatory Encounters	7.9 (9.4)	7.0 (9.2)	25.0 (21.1)	19.0 (16.1)	8.0 (8.7)	7.0 (7.8)	9.0 (9.5)	9.0 (9.4)
Recent Diagnosis History[g]								
Atrial Fibrillation/Flutter	5,898 (4.8%)	24,931 (3.7%)	6,495 (4.0%)	18,564 (1.6%)	7,666 (5.9%)	33,264 (5.8%)	994 (5.2%)	4,113 (4.7%)
Cancer	19,699 (15.9%)	110,913 (16.3%)	10,915 (6.7%)	44,275 (3.9%)	9,559 (7.4%)	41,800 (7.3%)	1,795 (9.4%)	7,857 (9.0%)
Cardiovascular Disease (prior)	11,106 (9.0%)	45,737 (6.6%)	71,590 (43.9%)	356,542 (31.4%)	70,594 (54.3%)	305,952 (53.2%)	9,898 (51.6%)	43,156 (49.4%)
Chronic Kidney Disease	2,708 (2.2%)	9,976 (1.5%)	11,032 (6.8%)	31,288 (2.8%)	6,920 (5.3%)	28,502 (5.0%)	633 (3.3%)	2,581 (3.0%)
Chronic Obstructive Pulmonary Disease	2,510 (2.0%)	9,900 (1.5%)	7,722 (4.7%)	17,425 (1.5%)	11,526 (8.9%)	41,377 (7.2%)	669 (3.5%)	2,771 (3.2%)
Diabetes Mellitus (any type)	17,954 (14.5%)	69,556 (10.2%)	18,788 (11.5%)	70,193 (6.2%)	14,899 (11.5%)	65,235 (11.3%)	1,680 (8.8%)	6,735 (7.7%)
Heart Failure	2,817 (2.3%)	8,119 (1.2%)	3,527 (2.2%)	7,939 (0.7%)	4,860 (3.7%)	20,158 (3.5%)	313 (1.6%)	1,156 (1.3%)
Hyperlipidemia	11,357 (9.2%)	53,950 (7.9%)	11,323 (6.9%)	47,962 (4.2%)	25,229 (19.4%)	112,708 (19.6%)	3,496 (18.2%)	15,654 (17.9%)
Hypertension	24,028 (19.4%)	93,727 (13.8%)	32,557 (20.0%)	131,158 (11.5%)	36,505 (28.1%)	166,816 (29.0%)	5,860 (30.6%)	24,202 (27.7%)
Neurological Disease	9,632 (7.8%)	14,729 (2.2%)	3,656 (2.2%)	8,115 (0.7%)	3,883 (3.0%)	13,795 (2.4%)	206 (1.1%)	767 (0.9%)
Venous Thromboembolism (prior)	1,314 (1.1%)	6,093 (0.9%)	4,233 (2.6%)	14,152 (1.2%)	2,438 (1.9%)	10,115 (1.8%)	216 (1.1%)	845 (1.0%)
Recent Dispensed Fills[h]								
Anticoagulant History	3,546 (2.9%)	9,600 (1.4%)	3,162 (1.9%)	8,991 (0.8%)	4,019 (3.1%)	17,790 (3.1%)	933 (4.9%)	3,673 (4.2%)
Antiplatelet History	2,626 (2.1%)	5,835 (0.9%)	5,875 (3.6%)	16,949 (1.5%)	5,484 (4.2%)	23,039 (4.0%)	1,582 (8.3%)	6,681 (7.7%)

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https://doi.org/10.2147/CLEP.S448980

https://doi.org/10.2147/CLEP.S448980 DovePress

Table 2 (Continued).

Panel B						
Characteristic[a]	**Netherlands[i]**		**Spain[j]**		**United States[k]**	
	Pre-Vaccine Availability	**Post-Vaccine Availability**	**Pre-Vaccine Availability**	**Post-Vaccine Availability**	**Pre-Vaccine Availability**	**Post-Vaccine Availability**
Total patients	45,673	107,054	307,499	204,923	272,065	753,454
Age (years)						
Mean (SD)	50.0 (18.5)	47.0 (18.1)	48.0 (18.8)	46.0 (18.4)	55.6 (17.5)	56.0 (16.9)
18–44 years	18,164 (39.8%)	50,231 (46.9%)	143,455 (46.7%)	99,756 (48.7%)	86,564 (31.8%)	236,287 (31.4%)
45–54 years	9,384 (20.5%)	20,600 (19.2%)	62,987 (20.5%)	41,552 (20.3%)	38,454 (14.1%)	105,290 (14.0%)
55–64 years	8,460 (18.5%)	17,556 (16.4%)	43,139 (14.0%)	28,581 (13.9%)	42,182 (15.5%)	114,298 (15.2%)
65–74 years	4,850 (10.6%)	10,489 (9.8%)	22,845 (7.4%)	17,110 (8.3%)	57,089 (21.0%)	171,320 (22.7%)
75–84 years	3,193 (7.0%)	5,897 (5.5%)	17,471 (5.7%)	10,632 (5.2%)	33,535 (12.3%)	95,921 (12.7%)
≥85 years	1,622 (3.6%)	2,281 (2.1%)	17,602 (5.7%)	7,292 (3.6%)	14,241 (5.2%)	30,338 (4.0%)
Female sex	26,507 (58.0%)	57,639 (53.8%)	171,804 (55.9%)	107,579 (52.5%)	151,017 (55.5%)	417,120 (55.4%)
Month of COVID-19 diagnosis						
March 2020	5,309 (11.6%)	–	61,716 (20.1%)	–	–	–
April 2020	5,600 (12.3%)	–	49,150 (16.0%)	–	14,127 (5.2%)	–
May 2020	1,889 (4.1%)	–	16,822 (5.5%)	–	15,926 (5.9%)	–
June 2020	1,366 (3.0%)	–	10,425 (3.4%)	–	22,176 (8.2%)	–
July 2020	1,319 (2.9%)	–	20,911 (6.8%)	–	38,414 (14.1%)	–
August 2020	1,534 (3.4%)	–	23,142 (7.5%)	–	26,537 (9.8%)	–
September 2020	3,790 (8.3%)	–	22,622 (7.4%)	–	24,648 (9.1%)	–
October 2020	13,679 (29.9%)	–	62,226 (20.2%)	–	42,288 (15.5%)	–
November 2020	11,187 (24.5%)	–	40,485 (13.2%)	–	87,949 (32.3%)	–
December 2020	–	13,937 (13.0%)	–	37,145 (18.1%)	–	110,215 (14.6%)

January 2021	–	10,073 (9.4%)	–	62,325 (30.4%)	–	102,643 (13.6%)
February 2021	–	5,657 (5.3%)	–	26,156 (12.8%)	–	42,638 (5.7%)
March 2021	–	9,505 (8.9%)	–	23,499 (11.5%)	–	36,121 (4.8%)
April 2021	–	12,329 (11.5%)	–	26,762 (13.1%)	–	34,545 (4.6%)
May 2021	–	4,870 (4.5%)	–	12,825 (6.3%)	–	18,380 (2.4%)
June 2021	–	1,588 (1.5%)	–	16,211 (7.9%)	–	10,513 (1.4%)
July 2021	–	6,595 (6.2%)	–	–	–	30,143 (4.0%)
August 2021	–	2,346 (2.2%)	–	–	–	81,365 (10.8%)
September 2021	–	1,900 (1.8%)	–	–	–	67,004 (8.9%)
October 2021	–	3,948 (3.7%)	–	–	–	44,611 (5.9%)
November 2021	–	18,050 (16.9%)	–	–	–	49,352 (6.6%)
December 2021	–	16,256 (15.2%)	–	–	–	125,924 (16.7%)
January 2022	–	–	–	–	–	–
February 2022	–	–	–	–	–	–
March 2022	–	–	–	–	–	–
April 2022	–	–	–	–	–	–
May 2022	–	–	–	–	–	–
June 2022	–	–	–	–	–	–
July 2022	–	–	–	–	–	–
August 2022	–	–	–	–	–	–
September 2022	–	–	–	–	–	–
Recent Encounters (mean, SD)[f]						
Number of Hospital Encounters	–	–	1.0 (5.8)	0.9 (5.4)	0.1 (0.5)	0.1 (0.5)
Number of Ambulatory Encounters	6.0 (7.9)	5.0 (6.3)	11.0 (12.6)	10.0 (12.9)	14.8 (19.4)	15.5 (18.8)

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https://doi.org/10.2147/CLEP.S448980

https://doi.org/10.2147/CLEP.S448980 DovePress

Table 2 (Continued).

Panel B						
Characteristic[a]	**Netherlands[i]**		**Spain[j]**		**United States[k]**	
	Pre-Vaccine Availability	**Post-Vaccine Availability**	**Pre-Vaccine Availability**	**Post-Vaccine Availability**	**Pre-Vaccine Availability**	**Post-Vaccine Availability**
Recent Diagnosis History[g]						
Atrial Fibrillation/Flutter	1,426 (3.1%)	2,497 (2.3%)	12,823 (4.2%)	6,930 (3.4%)	19,861 (7.3%)	54,528 (7.2%)
Cancer	3,696 (8.1%)	7,185 (6.7%)	21,230 (6.9%)	12,832 (6.3%)	33,201 (12.2%)	96,421 (12.8%)
Cardiovascular Disease (prior)	17,886 (39.2%)	35,557 (33.2%)	129,315 (42.1%)	77,051 (37.6%)	61,737 (22.7%)	172,992 (23.0%)
Chronic Kidney Disease	53 (0.1%)	88 (0.1%)	16,062 (5.2%)	8,495 (4.1%)	39,610 (14.6%)	104,342 (13.8%)
Chronic Obstructive Pulmonary Disease	1,533 (3.4%)	2,394 (2.2%)	10,462 (3.4%)	5,641 (2.8%)	30,803 (11.3%)	84,459 (11.2%)
Diabetes Mellitus (any type)	3,797 (8.3%)	6,863 (6.4%)	28,677 (9.3%)	17,323 (8.5%)	61,249 (22.5%)	165,313 (21.9%)
Heart Failure	938 (2.1%)	1,313 (1.2%)	9,056 (2.9%)	4,393 (2.1%)	21,430 (7.9%)	57,086 (7.6%)
Hyperlipidemia	2,512 (5.5%)	5,135 (4.8%)	50,070 (16.3%)	30,052 (14.7%)	119,851 (44.1%)	344,096 (45.7%)
Hypertension	7,075 (15.5%)	14,065 (13.1%)	62,047 (20.2%)	36,963 (18.0%)	125,942 (46.3%)	352,949 (46.8%)
Neurological Disease	665 (1.5%)	995 (0.9%)	11,736 (3.8%)	4,102 (2.0%)	18,184 (6.7%)	34,888 (4.6%)
Venous Thromboembolism (prior)	1,053 (2.3%)	1,986 (1.9%)	2,900 (0.9%)	1,695 (0.8%)	5,979 (2.2%)	16,372 (2.2%)
Recent Dispensed Fills[h]						
Anticoagulant History	1,207 (2.6%)	2,300 (2.1%)	6,592 (2.1%)	4,454 (2.2%)	19,219 (7.1%)	57,670 (7.7%)
Antiplatelet History	3,142 (6.9%)	5,674 (5.3%)	13,792 (4.5%)	8,429 (4.1%)	12,362 (4.5%)	35,517 (4.7%)

Notes: [a]Data presented as n (%) unless otherwise specified. [b]Included Canadian Network for Observational Drug Effect Studies (CNODES) data from British Columbia, Manitoba, and Ontario; the post-vaccine availability period included data from only British Columbia and Ontario. [c]Included data from Clinical Practice Research Datalink (CPRD) Aurum. [d]Included data from IQVIA Disease Analyzer Germany. [e]Included data from IQVIA Longitudinal Patient Data Italy. [f]Recent encounters assessed in the prior 365 days across all data sources. [g]Recent diagnosis history assessed in the prior 365 days in the US data sources, the prior 2 years for the Canadian data sources, and ever for the European data sources. [h]Recent dispensed fills assessed in the 183 to 3 days prior to COVID-19 diagnosis. [i]Included data from Integrated Primary Care Information (IPCI). [j]Included data from Information System for Research in Primary Care (SIDIAP) from Catalonia, Spain. [k]Included data from two national health insurers (Aetna; Humana, Inc.) and four regional integrated delivery systems (HealthPartners; Kaiser Permanente Colorado; Kaiser Permanente Northwest; Kaiser Permanente Washington) within the Food and Drug Administration Sentinel System; the post-vaccine availability period did not include Kaiser Permanente Washington.
Abbreviation: SD, standard deviation.

Table 3 90-Day Absolute Risk of Arterial and Venous Thromboembolism Events Among Ambulatory-Diagnosed Patients with COVID-19 Prior to and During COVID-19 Vaccine Availability, by Country

	Before COVID-19 Vaccine Availability			During COVID-19 Vaccine Availability		
	No. in Cohort	No. of Events	Absolute Risk (%) with 95% CI	No. in Cohort	No. of Events	Absolute Risk (%) with 95% CI
Arterial Thromboembolism						
CNODES (Canada)[a]	124,048	139	0.11 (0.09, 0.13)	678,907	684	0.10 (0.09, 0.11)
Clinical Practice Research Datalink Aurum (England)	163,103	477	0.29 (0.27, 0.32)	1,137,245	725	0.06 (0.06, 0.07)
IQVIA Disease Analyzer (Germany)	130,004	452	0.35 (0.32, 0.38)	575,160	1,667	0.29 (0.28, 0.30)
IQVIA Longitudinal Patient Data (Italy)	19,173	98	0.51 (0.42, 0.62)	87,319	313	0.36 (0.32, 0.40)
Integrated Primary Care Information (Netherlands)	45,673	254	0.56 (0.49, 0.63)	107,054	459	0.43 (0.39, 0.47)
Information System for Research in Primary Care (Spain)[b]	307,499	1,595	0.52 (0.49, 0.54)	204,923	1,033	0.50 (0.47, 0.54)
FDA Sentinel (United States)[c]	272,065	2,752	1.01 (0.97, 1.05)	753,454	7,801	1.04 (1.01, 1.06)
Venous Thromboembolism						
CNODES (Canada)[a]	124,048	287	0.23 (0.21, 0.26)	678,907	1,967	0.29 (0.28, 0.30)
Clinical Practice Research Datalink Aurum (England)	163,103	1,371	0.84 (0.80, 0.89)	1,137,245	2,837	0.25 (0.24, 0.26)
IQVIA Disease Analyzer (Germany)	130,004	387	0.30 (0.27, 0.33)	575,160	1,643	0.29 (0.27, 0.30)
IQVIA Longitudinal Patient Data (Italy)	19,173	127	0.66 (0.55, 0.79)	87,319	508	0.58 (0.53, 0.63)
Integrated Primary Care Information (Netherlands)	45,673	190	0.42 (0.36, 0.48)	107,054	361	0.34 (0.30, 0.37)
Information System for Research in Primary Care (Spain)[b]	307,499	1,132	0.37 (0.35, 0.39)	204,923	698	0.34 (0.32, 0.37)
FDA Sentinel (United States)[c]	272,065	2,175	0.80 (0.77, 0.83)	753,454	7,650	1.02 (0.99, 1.04)

Notes: [a]Included data from British Columbia, Manitoba, and Ontario before COVID-19 vaccine availability and British Columbia and Ontario during COVID-19 vaccine availability. [b]Included data from Catalonia, Spain. [c]Included data from two national health insurers (Aetna; Humana, Inc.) and four regional integrated delivery systems (HealthPartners; Kaiser Permanente Colorado; Kaiser Permanente Northwest; Kaiser Permanente Washington) before COVID-19 vaccine availability. Included data from two national health insurers (Aetna; Humana, Inc.) and three regional integrated delivery systems (HealthPartners; Kaiser Permanente Colorado; Kaiser Permanente Northwest) during COVID-19 vaccine availability.

Abbreviations: CI, confidence interval; CNODES, Canadian Network for Observational Drug Effect Studies; FDA, Food and Drug Administration.

https://doi.org/10.2147/CLEP.S448980 DovePress

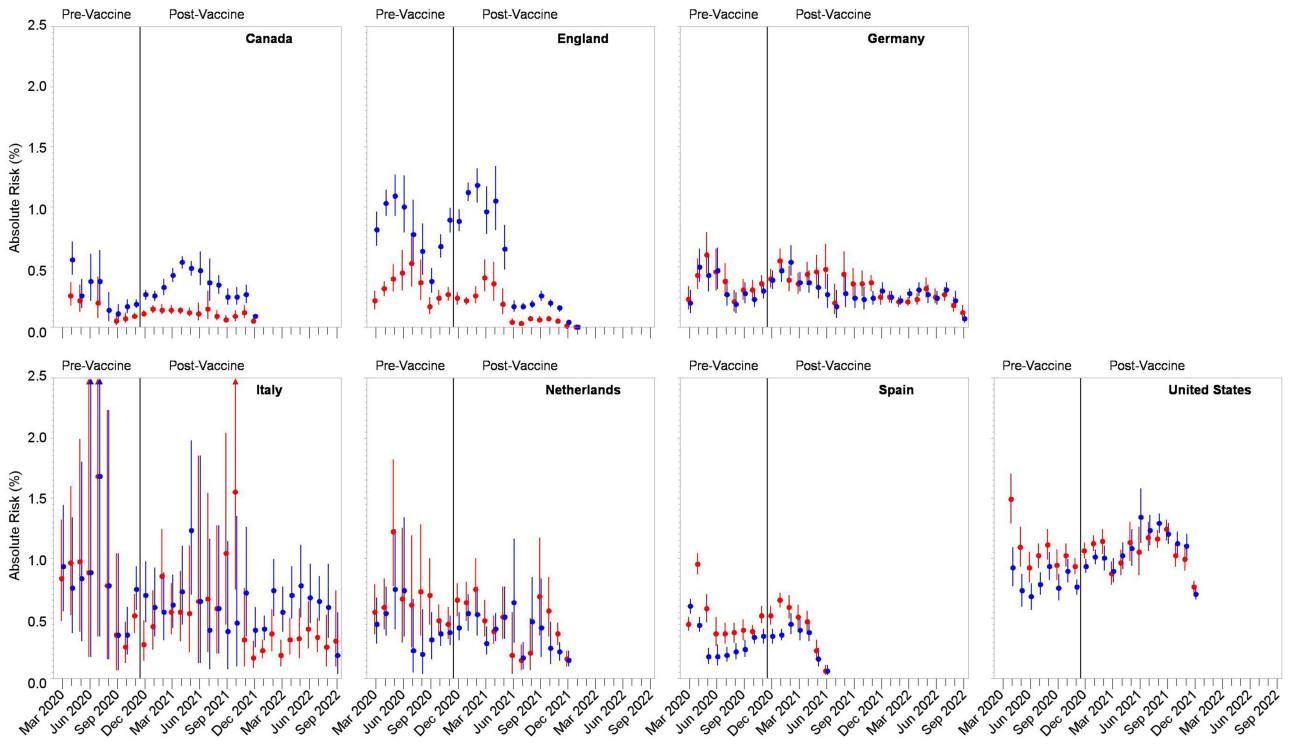

Figure 1 Country-level estimates (95% confidence intervals) of 90-day absolute risk of arterial (red) and venous (blue) thromboembolism events among patients initially diagnosed with COVID-19 in the ambulatory (ie, outpatient, emergency department, or institutional) setting, by month of diagnosis across the pre- and post-vaccine availability periods.

The 30-day risk of all-cause mortality following ATE or VTE varied across the countries before and during COVID-19 vaccine availability (Supplemental Table 3). Prior to vaccine availability, the 30-day risk of death after ATE ranged from 2.31% (95% CI, 1.16–4.09%) in England to 33.09% (95% CI, 25.35–41.57%) in Canada and after VTE ranged from 1.17% (95% CI, 0.67–1.89%) in England to 14.62% (95% CI, 13.16–16.18%) in the US. During vaccine availability, the 30-day risk of death after ATE ranged from 2.18% (95% CI, 1.05–3.97%) in the Netherlands to 22.81% (95% CI, 19.71–26.14%) in Canada and after VTE ranged from 1.69% (95% CI, 1.25–2.24%) in England to 18.12% (95% CI, 17.26–19.00%) in the US.

90-Day Risk of ATE and VTE with Hospital-Diagnosed COVID-19

We included 62,295 patients from Canada, Spain, and the US initially diagnosed with COVID-19 in the hospital before COVID-19 vaccines were available and 117,103 patients from these countries initially diagnosed with COVID-19 in the hospital during vaccine availability. The majority of hospital-diagnosed persons were ≥65 years of age and male both before and during COVID-19 vaccine availability (Supplemental Table 4). Baseline diagnoses that might affect the risk of thrombosis were prevalent among patients hospitalized with COVID-19 (Supplemental Table 4). For example, in the period before COVID-19 vaccine, the prevalence of hypertension among patients hospitalized for COVID-19 ranged from 52.9% in Spain to 87.4% in the US, and the prevalence of cancer ranged from 23.3% in Spain to 32.2% in Canada. After COVID-19 vaccine availability, the prevalence of hypertension among hospitalized patients ranged from 53.6% in Canada to 85.3% in the US, and the prevalence of cancer ranged from 25.9% in the US to 31.3% in Canada.

The 90-day absolute risk of ATE and VTE with hospital-diagnosed COVID-19 varied across the countries before and during vaccine availability (Supplemental Table 5). Prior to vaccine availability, the 90-day absolute risk of ATE ranged from 3.42% (95% CI, 3.15–3.72%) in Spain to 15.83% (95% CI, 15.48–16.18%) in the US. The 90-day absolute risk of VTE during this period ranged from 3.34% (95% CI, 3.06–3.63%) in Spain to 9.61% (95% CI, 9.33–9.90%) in the US. The risks were similar during vaccine availability. Within each country and during both periods, the 90-day risk of these events was higher for patients who were older and male (Supplemental Table 6). There was variability in the risk of ATE

and VTE observed among patients with hospital-diagnosed COVID-19 by month across the countries (Supplemental Figure 1 and Supplemental Table 7).

Prior to COVID-19 vaccine availability, the 30-day absolute risk of all-cause mortality after ATE ranged from 16.14% (95% CI, 13.13–19.52%) in Spain to 26.38% (95% CI, 21.07–32.25%) in Canada (Supplemental Table 8). The risks were similar during COVID-19 vaccine availability. The 30-day absolute risk of all-cause mortality after VTE before COVID-19 vaccine availability ranged from 9.33% (95% CI, 6.98–12.15%) in Spain to 17.95% (95% CI, 16.77–19.17%) in the US (Supplemental Table 8). During COVID-19 vaccine availability, the 30-day absolute risk of all-cause mortality after VTE ranged from 14.68% (95% CI, 10.26–20.09%) in Spain to 22.12% (95% CI, 21.32–22.93%) in the US.

Discussion

This study highlights a new collaboration among the regulatory authorities of Canada, Europe, and the US within the International Coalition of Medicines Regulatory Authorities that was established to evaluate real-world data on COVID-19-related topics of importance during the pandemic. This initial collaboration examined the epidemiology of ATE and VTE after COVID-19 diagnosis from representative samples across seven countries. This series of cohort studies showed that the 90-day absolute risk of ATE and VTE after initial diagnosis of COVID-19 in the ambulatory or hospital setting varied by country. There was variability in the risk of ATE and VTE by month across the countries among patients initially diagnosed with COVID-19 in the ambulatory or hospital setting. There was also variability across the countries in the 30-day risk of death after ATE or VTE among these patients.

Few studies have examined the risk of ATE or VTE among patients diagnosed with COVID-19 in the ambulatory or hospital setting across different countries. One cohort study of 909,473 non-hospitalized patients with COVID-19 identified between September 2020 and July 2021 in Germany, Italy, Netherlands, Spain, and the United Kingdom using the same data sources and similar inclusion criteria in the present study found that the 90-day incidence of ATE was 0.06–0.79%, and the 90-day incidence of VTE was 0.21–0.80%.[6] Our study, which included data from the five aforementioned countries as well as Canada and the US, found similar estimates of risk of ATE and VTE as those reported previously among the patients with ambulatory-diagnosed COVID-19.

Despite stratifying our analyses by the setting of initial COVID-19 diagnosis (ambulatory versus hospital setting), we observed substantial heterogeneity in the 90-day absolute risk of ATE and VTE and in the 30-day risk of all-cause mortality after a thrombotic event across the real-world data sources in this study. Such heterogeneity has been previously observed in an analysis of the incidence rates of VTE from eleven databases across six European countries from 2017 to 2020.[31] Due to the observed heterogeneity, we chose not to perform a meta-analysis and calculate pooled estimates of the absolute risk of thrombotic outcomes.[32] The heterogeneity may have been due to a variety of reasons. First, there were substantial differences in the prevalence of underlying comorbid conditions (eg, cardiovascular disease, hypertension, hyperlipidemia) that affect risk of ATE or VTE across the countries. There were also differences in the age distribution of the cohorts. Second, the countries had different underlying source data (administrative claims, EMR; Table 1) and utilized different diagnostic coding systems and practices, which might have affected outcome ascertainment. Third, the healthcare systems across the countries varied, which might have contributed to differences in the probability of recording thrombotic outcomes as well as COVID-19 treatment approaches. There may also be different levels of quality control or incentives for correct coding.[33] Fourth, data from Canada and the US evaluated ATE and VTE events based on hospital discharge diagnoses, whereas the European countries ascertained thromboses based on hospital discharge summaries. Finally, the SARS-CoV-2 variants in circulation varied across the countries and time periods studied.

Some countries' absolute risk of ATE and VTE decreased from the pre- to post-vaccine periods. A decrease in risk of ATE and VTE was observed in Spain and England in June 2021 and in the US in December 2021. These declines may have occurred because the majority of infections in Europe were among very young adults during summer 2021,[34] and because there was lower severity of acute disease associated with the omicron variant in the US.[35] Moreover, breakthrough SARS-CoV-2 infection among COVID-19-vaccinated persons has been associated with a reduced risk of thrombosis compared to persons with SARS-CoV-2 infection who were not previously vaccinated.[21,36,37]

This study has several potential limitations. First, misclassification of thrombotic outcomes was possible. Clinicians may have assigned ATE or VTE diagnoses based on clinical suspicion, since confirmatory tests might not have been able

to be performed due to isolation measures or overburdened resources. Second, some thrombotic events or deaths might have been missed due to delays in data availability. Third, there is the potential for selection bias due to different practices in COVID-19 testing across the countries and time periods. Fourth, we were unable to evaluate data on COVID-19 immunization status, since COVID-19 vaccination was not available for this study. However, publicly available data show that completeness of COVID-19 vaccination coverage varies across our study countries.[38] Fifth, mortality data were unavailable from Germany, and we might have incompletely ascertained out-of-hospital deaths due to delays in data availability. Finally, only unadjusted absolute risks of ATE and VTE were estimated.

Conclusion

In conclusion, our study demonstrates a new collaboration among the regulatory authorities of Canada, Europe, and the US to evaluate real-world data on COVID-19 and establishes an approach to generate real-world evidence during future public health crises. In this large scale, multi-country study, we found substantial heterogeneity in the 90-day absolute risk of ATE and VTE after COVID-19 diagnosis by country. There was also heterogeneity across the countries in the 30-day risk of death after an ATE or VTE event among patients diagnosed with COVID-19. Although analyses were stratified by setting of initial COVID-19 diagnosis, differences in the healthcare systems, prevalence of comorbidities in the study cohorts, and approaches to operationalizing the case definitions of ATE and VTE likely contributed to the heterogeneity in estimates of thrombotic risk across the countries.

Abbreviations

ATE, arterial thromboembolism; CI, confidence interval; CNODES, Canadian Network for Observational Drug Effects Studies; CPRD, Clinical Practice Research Datalink; DVT, deep venous thrombosis; EMA, European Medicines Agency; EMR, electronic medical record; FDA, Food and Drug Administration; GP, general practitioner; ICD-9-CA, International Classification of Diseases, Ninth Revision, Canadian Modification; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CA, International Classification of Diseases, Tenth Revision, Canadian Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IPCI, Integrated Primary Care Information; PE, pulmonary embolism; SIDIAP, Information System for Research in Primary Care; SNOMED, Systematized Nomenclature of Medicine; US, United States; VTE, venous thromboembolism.

Data Sharing Statement

The data generated in this study are not publicly available. In accordance with current European and national law, the data used in this study are only available for the researchers participating in this study. Thus, we are not permitted to distribute or make publicly available the data to other parties. Additionally, Sentinel uses a distributed data approach in which Data Partners maintain physical and operational control of their own electronic health data after transforming it into a common data model. Sentinel does not save, maintain, or post individual-level datasets in order to preserve patient privacy. However, researchers can request data from the various data sources utilized if they comply with the requirements established by that data source.

Ethics Approval and Informed Consent

In Canada, the research protocol was reviewed and approved by Health Canada and by the data custodian and/or research ethics board at each participating CNODES provincial data center. In Europe, the protocol for this research was reviewed by the European Medicines Agencies and approved by database-specific ethics or data access committees. In the US, this Sentinel project was a public health surveillance activity conducted under US Food and Drug Administration authority and was not subject to Institutional Review Board oversight.

Acknowledgments

VLR and NMC are joint first authors. JMP and DPA are joint senior authors. This study was made possible through data sharing agreements between the participating CNODES member research centers and the respective provincial governments of British Columbia, Ontario, and Manitoba.

The views expressed in this publication are those of the authors and do not necessarily reflect the official policy of the European Medicines Agencies, Health Canada, or United States Food and Drug Administration. No endorsement by the US Food and Drug Administration, Health Canada, the European Medicines Agency, collaborating organizations, funders or data providers is intended or should be inferred.

Funding

The Canadian Network for Observational Drug Effect Studies (CNODES) is a core network partner of CoLab and funded by CADTH (grant number C222 360). At the time of this study, CNODES was a collaborating center of the Drug Safety and Effectiveness Network (DSEN) and funded by the Canadian Institutes of Health Research (CIHR, grant numbers DSE-11856 and DSE-146021). Health Canada had no role in data collection, management, or analysis. This project was also supported by Task Order 75F40119F19001 under Master Agreement 75F40119D10037 from the US Food and Drug Administration (FDA). The FDA approved the study protocol, including statistical analysis plan, and reviewed and approved this manuscript. Coauthors from the FDA participated in the result interpretation and in the preparation and decision to submit the manuscript for publication. The FDA had no role in data collection, management, or analysis. The European portion of this project was supported by the European Medicines Agency (EMA) as a specific contract with Erasmus Medical Center, Rotterdam, the Netherlands, under the framework contract number EMA/2018/21/PE, Lot 3. The EMA approved the EU study protocol and reviewed and approved this manuscript. The EMA had no role in data collection, management, or analysis. Additional support was provided by the UK NIHR Oxford Biomedical Research Centre.

Disclosure

VLR III reports research grants to his institution from the US Food and Drug Administration (FDA) and the National Institutes of Health (NIH); consulting fees from Entasis, Takeda, and Urovant Sciences; and participation on the FDA Drug Safety and Risk Management Advisory Committee. NMC reports research funding from FDA via a Department of Health and Human Services (HHS) contract during the conduct of the study and funding from HPHCI (a non-profit organization that conducts work for government and private organizations, including pharmaceutical companies) outside the submitted work. RAH reports grants from FDA, NIH, and Merck. AMP reports royalties from UpToDate (including for an article on anticoagulation), consulting fees via advisory board from BioMarin LLC outside the submitted work, and speaker honorarium from the American Society of Hematology. DAD reports stock options in CVS Health. JLK reports unrelated research grants to her institution from Vir Biotechnology, Pfizer, Novartis, and the Centers for Disease Control and Prevention. PRR reports unrelated research grants to his institution from Chiesi, UCB, Amgen, Johnson & Johnson, Innovative Medicines Initiative, and the European Medicines Agency. KV reports unrelated research grants to her institution from Chiesi, UCB, Amgen, Johnson & Johnson, and the European Medicines Agency. DPA reports research grants to his institution from Amgen, Chiesi-Taylor, Lilly, Janssen, Novartis, and UCB Biopharma as well as consulting fees from Astra Zeneca and UCB Biopharma. The authors report no other conflicts of interest in this work.

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