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Major Cardiovascular Events After COVID-19, Event Rates Post-vaccination, Antiviral or Anti-inflammatory Therapy, and Temporal Trends: Rationale and Methodology of the Corona-VTE-Network Study

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Major cardiovascular events after COVID-19, event rates post-vaccination, antiviral or anti-inflammatory therapy, and temporal trends: Rationale and methodology of the CORONA-VTE-Network study

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is associated with excess risk of cardiovascular and thrombotic events in the early post-infection period and during convalescence. Despite the progress in our understanding of cardiovascular complications, uncertainty persists with respect to more recent event rates, temporal trends, association between vaccination status and outcomes, and findings within vulnerable subgroups such as older adults (aged 65 years or older), or those undergoing hemodialysis. Sex-informed findings, including results among pregnant and breastfeeding women, as well as adjusted comparisons between male and female adults are similarly understudied.

Methods: Adult patients, aged ≥18 years, with polymerase chain reaction-confirmed COVID-19 who received inpatient or outpatient care at the participating centers of the registry are eligible for inclusion. A total of 10,000 patients have been included in this multicenter study, with Brigham and Women's Hospital (Boston, MA) serving as the coordinating center. Other sites include Beth Israel Deaconess Medical Center, Anne Arundel Medical Center, University of Virginia Medical Center, University of Colorado Health System, and Thomas Jefferson University Health System. Data elements will be ascertained manually for accuracy. The two main outcomes are 1) a composite of venous or arterial thrombotic events, and 2) a composite of major cardiovascular events,

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defined as venous or arterial thrombosis, myocarditis or heart failure with inpatient treatment, new atrial fibrillation/flutter, or cardiovascular death. Clinical outcomes are adjudicated by independent physicians. Vaccination status and time of inclusion in the study will be ascertained for subgroup-specific analyses. Outcomes are pre-specified to be reported separately for hospitalized patients versus those who were initially receiving outpatient care. Outcomes will be reported at 30-day and 90-day follow-up. Data cleaning at the sites and the data coordinating center and outcomes adjudication process are in-progress.

Conclusions: The CORONA-VTE-Network study will share contemporary information related to rates of cardiovascular and thrombotic events in patients with COVID-19 overall, as well as within key subgroups, including by time of inclusion, vaccination status, patients undergoing hemodialysis, the elderly, and sex-informed analyses such as comparison of women and men, or among pregnant and breastfeeding women.

1. Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in significant morbidity and mortality worldwide. Alongside pulmonary parenchymal complications, COVID-19 is also associated with a range of cardiovascular complications, including acute myocardial infarction, cardiomyopathy, myocarditis/pericarditis, stroke, arrhythmias, and arterial and venous thromboembolism (VTE) [1–21]. The enduring nature of COVID-19, as it continues to persist at lower incidence with episodic peaks [22,23], emphasizes the need for further research to better understand its consequences.

The short- [3,24,25] and long-term [26,27] cardiovascular and thrombotic complications of COVID-19 have been under investigation since 2020 (Supplemental Figs. 1 and 2). Early in the pandemic, seminal studies evaluating short-term outcomes found that patients with COVID-

Table 1A
Studies reporting 30-day cardiovascular events post-COVID19.*

Study	Outcome(s)	Sample size	Percent female	Age (years)	Setting	Case/outcome ascertainment	Summary of findings
Wang et al [30], 2020	Cardiac arrhythmia	138	45.7	56†	Single center Inpatient	Detailed review of EHRs and ECGs	16.7 % of patients admitted with COVID-19 developed cardiac arrhythmia.
Zhou et al [31], 2020	HF	191	56.0	38.0‡	Multicenter Inpatient	Detailed review of EHRs using standardized data collection form¶	23 % of patients admitted with COVID-19 developed heart failure diagnosed via chest radiographs and CT scans.
Katsoularis et al [35], 2021	MI and stroke	86,472	57.0 %	48.0‡	Multicenter Inpatient, outpatient and post-discharge	ICD-9 and ICD-10 codes	COVID-19 is an independent risk factor for acute myocardial infarction and ischemic stroke, especially in the two weeks following symptom onset.
Piazza et al [16], 2020	AT and VTE, myocarditis, hospitalization for HF, new-onset AF	1114	54.1	50.6†	Multicenter Inpatient, Outpatient and post-discharge	Detailed review of EHRs using standardized data collection form¶	35.3 % of ICU patients with COVID-19 had arterial thrombotic and VTE events. ICU patients had high rates of heart failure exacerbation, new-onset atrial fibrillation, and myocarditis.
Daniels et al [29], 2021	Myocarditis	1597	39.6	N/A	Multicenter Outpatient	Prospective patient enrollment	Myocarditis occurred in 2.3 % of athletes diagnosed with COVID-19 and screened using cardiac magnetic resonance imaging.
Hockham et al [32], 2023	Cardiovascular complications (myocarditis, pericarditis, endocarditis, myocardial ischemia, arrhythmia, stroke, HF, PE)	11,167	40.0	68.0‡	Multicenter Inpatient	Detailed review of EHRs	Hospitalized female patients with COVID-19 were at lower risk of cardiovascular complications (13 %) compared with men (17 %).
Venturelli et al [33], 2021	Cardiovascular complications (cardiac ischemia, cardiac arrhythmia)	767	32.9	63.0†	Single center Inpatient	Detailed review of EHRs	Hospitalized COVID-19 patients had a higher incidence of cardiac complications such as arrhythmia, ischemia, and myocarditis.
Jiang et al [28], 2023	MACE§	1,934,294	55.9	45.2†	Multicenter Inpatient and outpatient	Unvalidated ICD-10 codes	MACE was observed in 0.7 % of all patients. A higher rate was observed among non-vaccinated patients (0.7 % of these patients) than fully-vaccinated patients (0.5 %).
Rosenblatt et al [34], 2023	New-onset AF	27,851	51.7	61.2‡	Multicenter Inpatient	Detailed review of EHRs	Incidence of new-onset AF was 5.4 %. The rate of major cardiovascular events was higher among patients with new-onset AF compared with no AF.

AF = atrial fibrillation; AHA = American Heart Association; AT = arterial thrombosis; CT = computed tomography; ECG = electrocardiography; EHR = electronic health record; HF = heart failure; ICD = international classification of diseases; ICU = intensive care unit; N/A = not applicable; PE = pulmonary embolism; VTE = venous thromboembolism.

* We only reported studies that came out early in the pandemic (until 05/31/2020) or others that had >500 patients. If a study did not report 30-day outcomes, in-hospital outcomes are reported.

† Mean age reported.

‡ Average median age reported.

§ Major adverse cardiovascular events, a composite of myocardial infarction, stroke, heart failure, cardiogenic shock, VTE, new-onset ventricular arrhythmia, new-onset atrial fibrillation or flutter, pericardial effusion, or tamponade, or aborted cardiac arrest.

¶ Outcomes were adjudicated.

19 who were hospitalized had a high incidence of fatal and nonfatal cardiovascular complications [5,6,10–19,21,28–37] (Tables 1A and 1B). The risk of VTE was particularly high in the intensive care unit, with pooled incidence rate of 27 % in a meta-analysis of early studies [38]. The increased risk of cardiovascular complications, including thromboembolic disease, has been observed to persist over a more prolonged period of follow-up beyond the initial 30 days post-infection [39–53] (Tables 2A and 2B). In some studies, patients with COVID-19 appeared to have a higher incidence of post-hospital venous thromboembolism within 90 days of hospital discharge [40,47], a finding that was not consistent across other studies [19].

However, important knowledge gaps persist and limit our understanding of these COVID-19-associated cardiovascular complications. Several of the existing studies were single center or had small sample sizes, limiting both the power to detect relevant signals, and the external validity of the findings [5,13,14,54–56]. The ensuing meta-analyses were affected by the wide clinical and statistical heterogeneity in these studies. Other studies used large-scale data sources; however, their analyses relied on administrative claims data or International Classification of Diseases (ICD) codes without patient-level validation of code accuracy [21,27,40,57–60]. Finally, a plethora of changes has occurred from the beginning of the pandemic, a period when much of the evidence related to cardiovascular complications of COVID-19 was generated. Limited high-quality data exist related to associations between prior vaccination status [21,28,48], use of anti-inflammatory therapies [61,62] or antiviral agents [63–65], and the incidence and types of cardiovascular events. Time trends for the cardiovascular event rates in patients with COVID-19-associated VTE have not been rigorously studied, either.

The CORONA-VTE-Network study is a large multicenter registry of

Table 1B
Studies reporting 30-day thrombotic events post-COVID-19.*

Study	Outcome (s)	Sample size	Percent female	Age (years)	Setting	Case/outcome ascertainment	Summary of findings
Klok et al [5], 2020	AT and VTE	184	24.0	64.0‡	Multicenter Inpatient	Prospective patient enrollment	31 % incidence of thrombotic complications among ICU patients with COVID-19 despite thromboprophylaxis.
Lodigiani et al [13], 2020	AT and VTE	388	32.0	66.0†	Single center Inpatient	Detailed review of EHRs using standardized data collection form§	Risk of thrombotic events, especially VTE, was significantly increased among patients admitted with COVID-19.
Middeldorp et al [14], 2020	VTE	198	34.0	61.0‡	Single center Inpatient	Detailed review of EHRs using standardized data collection form§	Incidence of VTE is high among hospitalized patients with COVID-19 (6 %, 9.%, and 9.% at 7, 14, and 21 days), especially those in the ICU (26 %, 47 %, and 59 % at 7, 14, and 21 days).
Bilaloglu et al [10], 2020	AT, VTE	3334	39.6	64.0†	Multicenter Inpatient	Chart review for covariates, NLP identified outcomes, confirmed by chart review	Patients with COVID-19 have a high risk of thrombosis (arterial or venous, [11.5 %]), especially among patients in the ICU (29.4 %).
Fauvel et al [12], 2020	PE	1240	41.9	64.0‡	Multicenter Inpatient	Detailed review of EHRs using standardized data collection form	Patients with COVID-19 who were given low-intensity or full-intensity dose prophylactic anticoagulation had a significantly decreased incidence of pulmonary embolism (odds ratio of 0.83 and 0.87, respectively) than those patients who received no anticoagulation.
Helms et al [36], 2020	AT and VTE	150	29.6	63.0†	Multicenter Inpatient	Prospective patient enrollment	Compared to non-COVID-19 ARDS patients in the ICU, COVID-19 ARDS patients developed significantly more thrombotic complications, especially pulmonary embolisms (11.7 vs. 2.1 %, $p < 0.008$).
Qureshi et al. [37], 2021	AT	8163	47.0	54.6‡	Multicenter Inpatient	ICD-9 and ICD-10 codes	The occurrence of acute ischemic stroke among hospitalized COVID-19 patients (1.3 %) was found to be similar to that among hospitalized patients without COVID-19 (1.0 %).
Piazza et al [16], 2020	AT and VTE	1114	54.1	50.6†	Multicenter Inpatient, outpatient and post-discharge	Detailed review of EHRs using standardized data collection form§	The rate of a major arterial or venous thromboembolic event was 16.5 % among patients admitted with COVID-19.
Roberts et al [17], 2020	VTE	2863	N/A	N/A	Multicenter Inpatient and post-discharge	Detailed review of EHRs	Odds ratio for post-discharge hospital associated. VTE following hospitalization with COVID-19, compared with 2019 medical admissions, was 1.6 (95 % confidence interval, 0.8–3.1).
Kaptein et al [18], 2021	AT and VTE	947	36.0	66.0‡	Multicenter Inpatient	Detailed review of EHRs using standardized data collection form§	Compared with the first wave of COVID-19 (February 24 to April 26, 2020), rates of VTE and arterial thrombotic events remained comparable among patients admitted with COVID-19 in the second wave (September 1 to November 30, 2020).
Roubinian et al [19], 2021	VTE	220,588	59.4	47.1‡	Multicenter Inpatient, Outpatient and post-discharge	ICD-10 codes	30-day VTE incidence is not significantly increased among outpatients with COVID-19 (1.8 %) compared with patients without COVID-19 (2.2 %).
Xie et al [21], 2022	VTE	18,818	58.3	67.8‡	Multicenter Outpatient	Unvalidated ICD-10 codes	Ambulatory COVID-19 infection substantially increases the risk of VTE, a risk greatly reduced in fully vaccinated patients with breakthrough infection.

AHA = American Heart Association; ARDS = acute respiratory distress syndrome; AT = arterial thrombosis; EHR = electronic health record; ICD = international classification of diseases; ICU = intensive care unit; N/A = not applicable; NLP = natural language processing; PE = pulmonary embolism; UK = United Kingdom; VTE = venous thromboembolism.

* We only reported studies that came out early in the pandemic (until 05/31/2020) or others that had $N > 500$; if a study did not report 30-day outcomes, in-hospital outcomes are reported.

† Average median age reported.

‡ Mean age reported.

§ Outcomes were adjudicated.

Table 2A
Studies reporting 90-day or longer follow-up for cardiovascular events post-COVID-19.*

Study	Outcome(s)	Sample size	Percent female	Age (years)	Setting	Case/outcome ascertainment	Summary of findings
Al-Aly et al [39], 2021	CV complications including cardiac dysrhythmias and HF	5,064,270	12.1	59.1†	Multicenter Outpatient	ICD-10 codes	Patients had excess burden of CV complications in the 6-month period post-COVID, including cardiac dysrhythmias (8.41 per 1000 patients) and heart failure (3.94 per 1000 patients).
Ayoubkhani et al [42], 2021	MACE§	47,780	45.0	65.0†	Multicenter Inpatient and post-discharge	ICD-10 codes	Over a mean follow-up of 140 days post-discharge, COVID-19 patients have increased rates of MACE (66 per 1000 person years) compared with the general population.
Daugherty et al [43], 2021	Arrhythmia, HF, myocarditis, CAD, ischemic or hemorrhagic stroke, VTE	18,969,886	50.0	42.5†	Multicenter Inpatient, outpatient and post-discharge	ICD-10 codes	There is excess risk of developing CV complications 21 days after acute COVID-19 diagnosis, especially among admitted patients, compared with a matched cohort of patients without COVID-19. Follow-up continued up to a diagnostic event, disenrollment from the insurance plan or end of the study (10/31/2020), whichever occurred first.
Lund et al [41], 2021	VTE, myocarditis, AT, stroke	89,877	63.2	43.0‡	Multicenter Inpatient	ICD-10 codes	Over a 6-month follow-up period, there was an increased risk of VTE diagnosis among patients with COVID-19 compared with those without (RR: 1.77, 95 % CI: 1.09–2.86).
Al-Aly et al [44], 2022	CV complications (CAD, AF, HF, VTE)	13,482,547	9.6	63.4†	Multicenter Inpatient, Outpatient and post-discharge	ICD-10 codes	Increased rates of CV complications at 6-month follow-up among vaccinated patients with breakthrough infection compared with a contemporary control group (HR: 1.74, 95 % CI: 1.66–1.83). Lower rates of CV complications among patients with breakthrough infection compared with unvaccinated patients was observed (HR: 0.87, 95 % CI: 0.78–0.96).
Islam et al [45], 2022	MACE¶	16,939	45.4	61.6†	Multicenter Inpatient	Detailed review of EHRs	Patients living in socially vulnerable communities and hospitalized with COVID-19 had higher risk of MACE compared with less vulnerable communities, independent of race and ethnicity (OR: 1.26 [95 % CI, 1.05–1.50]; $P = 0.01$).
Ortega-Paz et al [46], 2022	AF and HF	4427	46.1	60.3†	Multicenter Inpatient, Outpatient and post-discharge	Detailed review of EHRs using standardized data collection form‖	Patients with COVID-19 had a higher 1-year rate of atrial fibrillation (HR: 2.27, 95 % CI: 1.33–3.86) and heart failure hospitalization (HR: 2.27, 95 % CI: 1.20–4.28) compared with patients without COVID-19.
Xie et al [40], 2022	Dysrhythmia, myocarditis, pericarditis, ischemic heart disease and VTE	11,650,818	9.6	63.1†	Multicenter Inpatient, Outpatient and post-discharge	ICD-10 codes	The 1-year rates of ischemic heart disease, pericarditis, myocarditis, VTE and dysrhythmias are significantly higher in COVID-19 survivors compared with patients without COVID-19.

AHA = American Heart Association; AT = arterial thrombosis; CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; ICD = international classification of diseases; MI = myocardial infarction; OR = odds ratio; RR = risk ratio; US = United States; VTE = venous thromboembolism.

* We only reported studies that came out early in the pandemic (until 05/31/2020) or others that had $N > 500$.

† Mean age reported.

‡ Average median age reported.

§ Major adverse cardiovascular events, a composite of myocardial infarction, heart failure, stroke, and arrhythmia.

¶ Major adverse cardiovascular events, a composite of MI, stroke, new-onset HF, cardiogenic shock, and death.

‖ Outcomes were adjudicated.

patients with COVID-19, with detailed patient-level data entry and independent outcome adjudication, designed to address these gaps in knowledge. The current manuscript summarizes the rationale and methodology of the registry.

2. Methods

2.1. Main features of study design

CORONA-VTE-Network is a multicenter study designed to include 10,000 patients from multiple community and referral hospitals. Patients will be included from the Mass General Brigham Health system (that includes Brigham and Women's Hospital, Massachusetts General Hospital, and several community hospitals). Other participating centers included the Beth Israel Deaconess Medical Center, Anne Arundel Medical Center, University of Virginia Medical Center, University of Colorado Health System, and Thomas Jefferson University Health System. Institutional review board approval was sought and obtained at all participating centers. Fig. 1 summarizes the breakdown of patients per study sites and their site-level demographic characteristics. Data have been and continue to be collected by trained abstractors through detailed review of electronic health records (EHRs).

Table 2B
Studies reporting 90-day or longer follow-up for thrombotic events post-COVID-19.*

Study	Outcome(s)	Sample size	Percent female	Age (years)	Setting	Case/outcome ascertainment	Summary of findings
Giannis et al [49], 2021	AT and VTE	4906	46.3	61.7‡	Multicenter Post-discharge	Prospective inclusion of consecutive patients	Over a mean follow-up period of 92 days, VTE and AT occurred post-discharge among respectively 1.55 % and 1.71 % of patients with COVID-19. Post-discharge anticoagulation reduced the risk by 46 %.
Rashidi et al [53], 2021	VTE	1529	45.6	56†	Multicenter Post-discharge	Prospective inclusion of consecutive patients	Within 45 days of discharge, 0.2 % of COVID-19 patients developed symptomatic VTE.
Kim et al [48], 2022	Acute myocardial infarction and ischemic stroke	231,037	52.6	52.9†	Multicenter Inpatient, outpatient and post-discharge	ICD-10 codes	Complete vaccination status is associated with a decreased rate of acute myocardial infarction (HR: 0.48, 95 % CI: 0.25–0.94) and ischemic stroke (HR: 0.40, 95 % CI: 0.26–0.63) after breakthrough COVID-19 infection, compared with unvaccinated patients.
Katsoularis et al [52], 2022	VTE	1,057,174	51.0 %	40.2‡	Multicenter, Inpatient, outpatient and post-discharge	ICD-9 and ICD-10 codes	Compared to COVID-19 negative patients, COVID-19 positive patients had an increased risk of DVT up to three months after diagnosis and PE up to six months.
Ortega-Paz et al [46], 2022	AT and VTE	4427	46.1	60.3†	Multicenter Inpatient, outpatient and post-discharge	Detailed review of EHRs using standardized data collection form§	The 1-year rates of VTE and AT were significantly higher among COVID-19 patients compared with patients without COVID-19 (HR: 9.33, 95 % CI: 2.93–29.70, and HR: 2.26, 95 % CI: 1.02–4.99).
Xie et al [40], 2022	VTE	11,650,818	9.6	63.1‡	Multicenter Inpatient, outpatient and post-discharge	ICD-10 codes	The 1-year rate of VTE is significantly higher among COVID-19 survivors compared with patients without COVID-19 (HR: 2.39, 95 % CI: 2.27–2.51).
Roubinian et al [47], 2023	VTE	63,920	56.0	59.0‡	Single center Post-discharge	ICD-10 codes	90-day post-discharge VTE among unvaccinated COVID-19 patients (1.6 %) was higher compared with vaccinated COVID-19 patients (1.2 %), whose rate was higher than COVID-19 negative patients (0.7 %). COVID-19 patients had a higher incidence of VTE in the Delta variant period compared with pre-Delta or the Omicron variant periods.

AT = arterial thrombosis; CI = confidence interval; HR = hazard ratio; ICD = international classification of diseases; RCT = randomized controlled trial; US = United States; VTE = venous thromboembolism.

* We only reported studies that came out early in the pandemic (until 05/31/2020) or others that had N > 500.

† Average median age reported.

‡ Mean age reported.

§ Outcomes were adjudicated.

2.2. Patients

Adult patients, aged ≥18 years, with reverse transcriptase polymerase chain reaction (RT-PCR) confirmed COVID-19 at participating sites of CORONA-VTE-Network were eligible for inclusion (Table 3).

Before the CORONA-VTE-Network population was chosen and data collection was completed, 3100 patients were recruited from the MGB sites for an earlier phase of this study (CORONA-VTE) [16]. Inclusion of subsequent patients from MGB was done from a random sample of patients in the MGB health system such that their COVID-19 status (inpatient vs outpatient) was relatively proportionate to the initial sample. The inpatient cohort consisted of symptomatic patients who were already admitted at the time of COVID-19 diagnosis as well as patients who were admitted within 1 day after testing positive for COVID-19. The outpatient cohort consisted of COVID-19 positive patients who were not admitted to the hospital within 1 day of their diagnosis.

2.3. Key variables and covariates

Age, sex, and race/ethnicity, co-morbid conditions, patient location at the time of entering the study (inpatient [including specific designation for intensive care] vs outpatient), risk factors for venous and arterial thrombotic events, co-treatments such as antiviral and anti-inflammatory therapies, and vaccination status will be captured. Supplemental Table 1 includes a list of some of the variables captured in CORONA-VTE-Network.

2.4. Outcomes

The CORONA-VTE Network study has two main outcomes. First is time to first event for VTE and arterial thrombotic events. The second main outcome is the time to first event for adverse cardiovascular events, a composite of venous or arterial thrombosis, myocarditis or heart failure with inpatient treatment, new atrial fibrillation/flutter, or cardiovascular death. Table 4 and Supplemental Table 2 summarize the operational definitions of all study outcomes. All outcomes will be adjudicated by independent physicians using these standard definitions. Outcomes will be reported both at 30-day and 90-day follow-up.

2.5. Statistical considerations

For primary analysis, we will report outcomes separately among inpatients and outpatients.

For basic characteristics and co-morbidities of included patients, categorical variables will be reported with frequency counts and percentages, and continuous variables will be reported with mean and standard deviation. For reporting the incidence of cardiovascular events and thrombotic events, point estimates and 95 % confidence intervals will be estimated, using subdistribution hazards that account for non-cardiovascular and non-thrombotic death as competing risks, respectively.

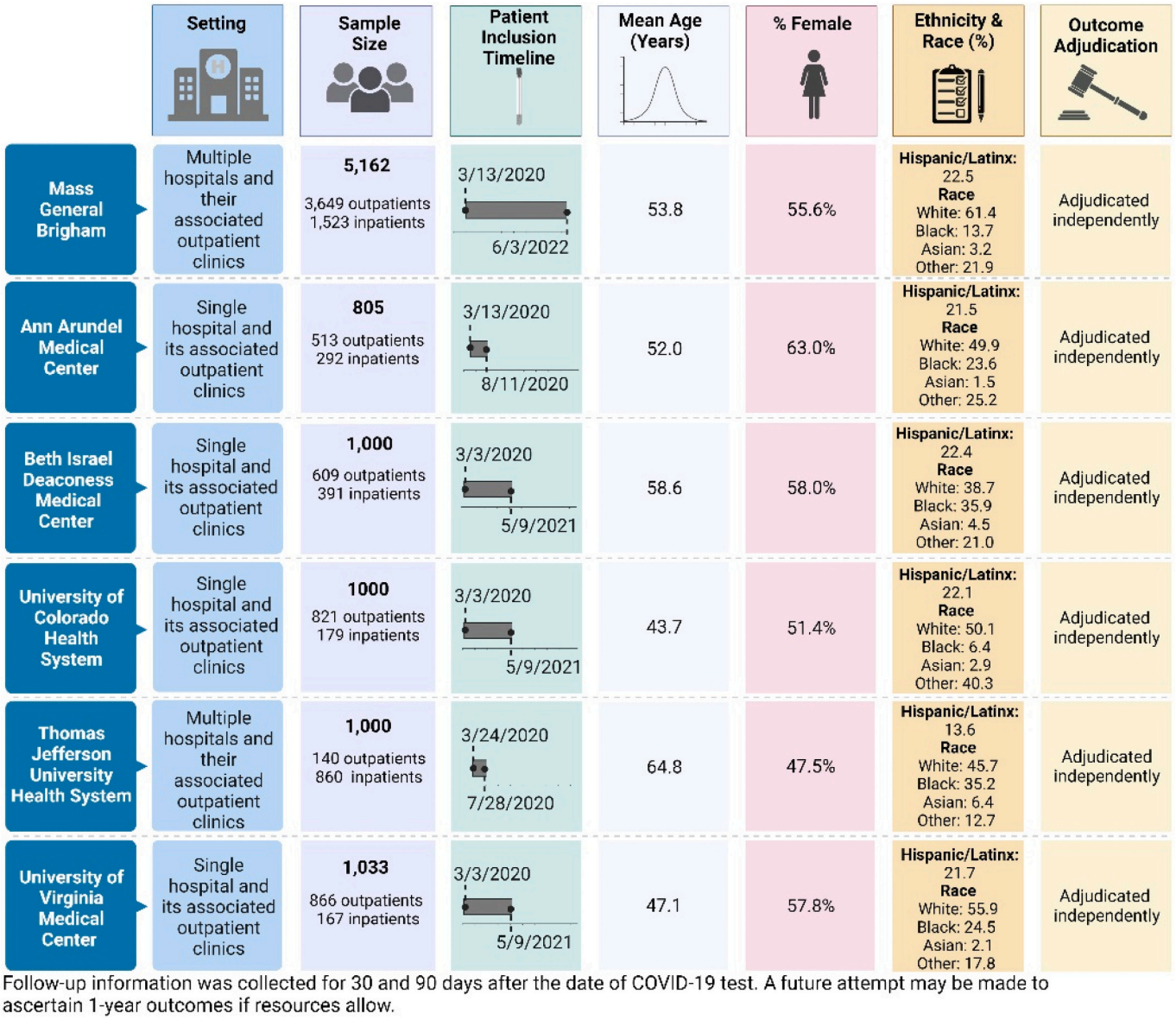

Fig. 1. Key features of study centers in the CORONA-VTE-Network. COVID-19 = Coronavirus disease 2019.

Table 3
Study eligibility criteria.

Inclusion criteria	Exclusion criteria
Age ≥ 18 years*	Expression of lack of consent for data being used for research purposes
First Positive RT-PCR for COVID-19 (or equivalent test†) between 3/03/2020 and 6/03/2022	Lack of confirmed COVID-19
Inpatient or outpatient management of COVID-19 infection‡	
Receiving care at one of the collaborating centers of CORONA-VTE-Network	

RT-PCR = reverse transcriptase polymerase chain reaction.
* Pregnant/breastfeeding women were also eligible.
† Antigen test as a first test acceptable, only if subsequently confirmed by RT-PCR.
‡ Self-quarantine is considered outpatient management.

For this multicenter study, the comparison of outcomes across subgroups (such as women vs men, see below) will be reported in unadjusted models. Subsequently, outcomes will be compared by mixed effects Cox regression (frailty) models with random intercepts for enrolling sites, and with adjustment of clinical covariates including age, race, and co-morbidities as well as subgroup indicators. Hazard ratios and their confidence intervals will be used for evaluating the differences.

For assessment of time trends, the data will be broken down into several time windows. The decomposition is planned to use important health policy issue dates to partition each time window with sufficient representative sample size for statistical tests. Two-sample proportion test will be used for comparing the event rates between any two windows. Cochran–Armitage test for trend will be used to detect the presence of an association between group-level incidence and time.

A landmark analysis has been pre-specified to assess the events that accrue only in the late phase of follow-up. For that analysis, day 30 will be considered the landmark time, and events from day 31 will be captured for analysis.

Table 4
Main study outcomes.

Outcome	Definition
DVT	Upper or lower extremity deep vein thrombosis confirmed with ultrasonography, computed tomography, or venography.
PE	Pulmonary embolism confirmed by computer tomography or pulmonary angiography.
Superficial vein thrombosis	Any thrombosis in a superficial venous system.
Catheter- or device-related thrombosis	Any arterial or venous thrombosis associated with a catheter or device (dialysis catheter, arterial line, central line, pacemaker lead, etc.).
MI*	Defined by the presence any two of the following: Signs or symptoms typical of myocardial infarction, abnormal electrocardiographic findings, and elevated cardiac biomarkers (CK-MB or Troponins I or T).
Stroke/TIA	Stroke: Sudden onset of neurologic deficits >24 h as confirmed by neuroimaging. TIA: transient episode of neurological deficits, caused by focal brain ischemia without infarction, that fully resolve within 24 h.
Major adverse limb event*	Sudden decrease in limb perfusion that may threaten limb viability.
Cardiovascular death	Death specifically due to PE, MI, stroke, or other cardiovascular causes.
All-cause mortality	Death due to any cause.
Major bleeding	Overt bleeding that is associated with a decrease in the hemoglobin level ≥ 2 g/dL, leads to transfusion ≥2 units of packed red blood cells, occurs in a critical site, or contributes to death, as defined by the ISTH criteria [72].
Clinically-relevant non-major bleeding	Overt bleeding that does not meet the criteria for major bleeding but that is associated with the need for medical intervention or impairment of activities of daily living, as defined by the ISTH criteria [73].
DIC*	Disseminated intravascular coagulation: defined by the criteria of the ISTH [74].
Thrombocytopenia	Platelet count <150,000/μL.
Heart failure hospitalization*	Admission for heart failure as defined by worsening heart failure symptoms and/or laboratory testing evidence of heart failure.
Non-MI coronary revascularization	Coronary artery bypass grafting, angioplasty, atherectomy, brachytherapy, or stenting outside of the setting of acute coronary syndrome.
Myocarditis*	Signs or symptoms of myocarditis and abnormal ECG or Holter monitor results; elevated troponin T/troponin I; or confirmational imaging via cardiac magnetic resonance, echo, or angiography.
New atrial fibrillation/flutter	ECG, telemetry or Holter monitor-detected atrial fibrillation or atrial flutter.

CK-MB = creatinine kinase-myocardial band; DIC = disseminated intravascular coagulation; DVT = deep vein thrombosis; ECG = electrocardiogram; ISTH = International Society on Thrombosis and Hemostasis; MI = myocardial infarction; PE = pulmonary embolism; TIA = transient ischemic attack.

* Refer to Supplemental Table 2 in the appendix for expanded definition. For patients included from Mass General-Brigham Health System, all outcomes will be adjudicated by two independent physicians who have access to detailed medical records, and in case of discrepancy, by a third physician. Outcomes for patients from other centers will be adjudicated by independent physicians, as well.

2.5.1. Main subgroup analyses of interest

All main analyses will be reported separately for hospitalized patients versus those who were receiving outpatient care at the time of COVID-19 diagnosis. Other particular clinical subgroups of interest include patients with versus those without prior vaccination, findings in those receiving vs those not receiving antiviral treatment, older adults (aged ≥65 years) vs younger patients, patients undergoing hemodialysis, patients with active cancer, and those with underlying cardiovascular diseases. We will also assess the unadjusted and multivariable adjusted findings in ethno-racial subgroups. Sex-informed pre-specified analyses include unadjusted and adjusted comparison of cardiovascular and thrombotic events in women vs men and in pregnant and breastfeeding women. Another subgroup of interest is patients admitted to the ICU, for whom we will be separately reporting the cardiovascular and thrombotic outcomes.

2.5.2. Sensitivity analysis

A sensitivity analysis will be performed with site reported vs adjudicated outcomes on data from MGB sites. We will also explore the sensitivity of findings per each particular enrolling site.

3. Results

Of 10,000 planned patients, 5162 will be included from MGB. The remaining patients will be recruited from Beth Israel Deaconess Medical Center (N = 1000), Anne Arundel Medical Center (N = 805), University of Virginia Medical Center (N = 1033), University of Colorado Health System (N = 1000), and Thomas Jefferson University Health System (N = 1000). Average age and sex distribution of patients across the centers have been recently obtained and are summarized in Fig. 1.

4. Discussion

The CORONA-VTE Network study is positioned to generate much-needed knowledge about short- and longer-term cardiovascular and thrombotic complications of COVID-19 through detailed individual patient-level data collection from 10,000 patients from 2020 through 2022 in a large multicenter study with independent clinical outcomes adjudication. A key goal of CORONA-VTE-Network is to provide a more contemporary estimate of event rates, compared with most of the earlier studies that provided estimates from early 2020. Furthermore, event rates will be assessed based on vaccination status, use of antiviral and anti-inflammatory therapies, and within vulnerable subgroups such as a pregnant or breastfeeding women, the elderly, and patients with end-stage renal disease. Time trends in incidence of cardiovascular and thrombotic events will also be assessed (Fig. 2).

Some previous seminal studies examining cardiovascular and thrombotic outcomes in COVID-19 were predominantly limited to single centers, had small sample sizes, only focused on the period of hospitalization, and primarily described demographics, SARs-CoV-2 variants, and management of patients impacted by the first surge of the pandemic [5,13,14,54,66]. In contrast, the CORONA-VTE-Network builds upon the previous CORONA-VTE registry that focused on a MGB health system data [16]. The Network includes healthcare centers across the United States over a broad time interval and experience during the COVID-19 pandemic, resulting in a large sample size and geographic diversity. This design will increase the study's power to detect relevant signals and to assess time trends. In addition, the CORONA-VTE-Network includes patients from diverse ethno-racial backgrounds and care settings such as outpatients, patients admitted to the non-intensive care wards and those admitted to the ICU, compared with studies focused on specific care locations [41].

Careful manual ascertainment of cases and adjudication of clinical outcomes based on objective evidence are two additional important features of CORONA-VTE-Network. Compared with studies from large databases that mostly rely on unvalidated ICD-10 codes and administrative claims data [21,27,39,40,67], our study uses trained abstractors who manually reviewed individual cases to verify COVID-19. More importantly, clinical outcomes were documented based on pre-specified objective clinical criteria which will be subsequently adjudicated by independent physicians. This method has superior accuracy and validity compared with use of ICD-10 codes, which in many cases have not been validated for the intended purposes. The CORONA-VTE-Network also encompasses distinct features compared with other COVID-19 registries evaluating cardiovascular outcomes [29,49,67,68]. The CORONA-VTE-Network emphasizes a centralized quality control and monitoring system and independent outcome adjudication, ensuring that the data are collected uniformly across all study sites and adhering to protocol (Fig. 3). In addition, we also captured data on different surge periods,

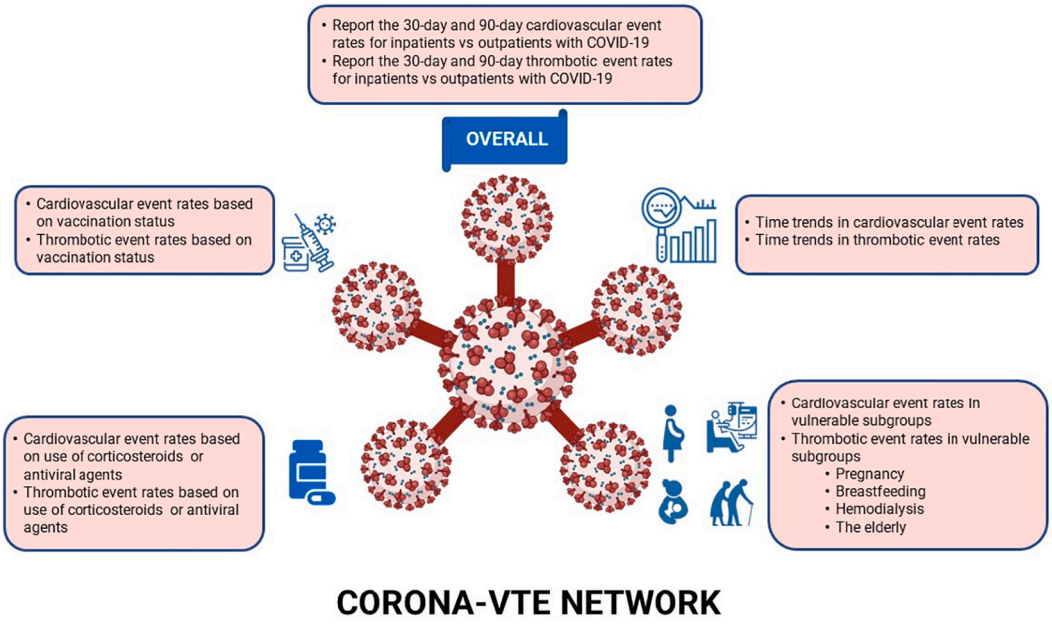

Fig. 2. Main objectives of the CORONA-VTE network study. COVID-19 = Coronavirus disease 2019.

vaccination status, and use of anti-inflammatory therapies and antiviral agents, all of which have yet to be well-detailed in cardiovascular and thrombosis studies of COVID-19.

Assessment of clinical outcomes at 30-day and 90-day follow-up will be complementary. Thirty-day cardiovascular and thrombotic outcomes will provide clearer inference of acute complications, whereas 90-day outcomes may also include those that accrue more steadily over time. Even though CORONA-VTE-Network will not directly assess post-acute COVID-19 (long-COVID), it is conceivable that patients who develop such events within 90 days are more likely to experience durable sequalae of COVID-19, including long-COVID [69,70].

Despite its strengths outlined above, we acknowledge the limitations of the CORONA-VTE-Network study. First, this study relies on data from electronic health records. Prospective patient enrollment with dedicated data collection would have been resource intensive and cost-prohibitive for the database size that CORONA-VTE-NETWORK aims to achieve. The EHRs available for the study include the medical notes, laboratory tests, and detailed imaging studies needed for ascertainment of the required data elements. This, in fact, is superior to data capture by ICD codes (which frequently have uncertain validity and reliability) [71] that have been used in the majority of other existing large studies. The laboratory tests are limited to those obtained for routine care. However, they include many of the clinically relevant tests, such as renal function, hemoglobin, white blood cell count, and others. We should also acknowledge that resource limitations did not allow for study-specific collection of biomarkers. However, for the subset of patients at MGB, the investigators are considering the option of linking the data to an existing biobank from MGB participants. In addition, at the current stage, the maximum follow-up period for patients is 90 days, although a longer follow-up may be planned in the future, contingent on availability of additional funding.

In conclusion, the CORONA-VTE-Network study will provide contemporary information related to adjudicated cardiovascular and thrombotic events in patients with COVID-19, including vaccination status, use of corticosteroid and antiviral therapy, and within vulnerable subgroups such as pregnant and breastfeeding women, the elderly, and those with end-stage renal disease.

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Declaration of competing interest

Dr. Bikdeli is supported by a Career Development Award from the American Heart Association and VIVA Physicians (#938814) for the PE-EHR+ study. Dr. Bikdeli was supported by the Scott Schoen and Nancy Adams IGNITE Award, and is supported by the Mary Ann Tynan Research Scientist award from the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital, and the Heart and Vascular Center Junior Faculty Award from Brigham and Women's Hospital. Dr. Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters. Mr. Fanikos has served as a consultant to Pfizer, AstraZeneca, and Mallinckrodt. Drs. Bonaca, Hsia and Nehler receive salary support from CPC, a non-profit academic research organization affiliated with the University of Colorado, that receives or has received research grant/consulting funding between February 2021 and February 2023 from the following organizations: Abbott Laboratories, Adamis Pharmaceuticals Corporation, Agios Pharmaceuticals, Inc., Alexion Pharma, Alnylam Pharmaceuticals, Inc., Amgen Inc., Angionetics, Inc., ARCA Biopharma, Inc., Array BioPharma, Inc., AstraZeneca and Affiliates, Atentiv LLC, Audentes Therapeutics, Inc., Bayer and Affiliates, Beth Israel Deaconess Medical Center, Better Therapeutics, Inc., Boston Clinical Research Institute, Bristol-Meyers Squibb Company, Cambrian Biopharma, Inc., Cardiol Therapeutics Inc., CellResearch Corp., Cook Medical Incorporated, Covance, CSL Behring LLC, Eidos Therapeutics, Inc., EP Trading Co. Ltd., EPG Communication Holdings Ltd., Epizon Pharma, Inc., Esperion Therapeutics, Inc., Everly Well, Inc., Exicon Consulting Pvt. Ltd., Faraday Pharmaceuticals, Inc., Foresee Pharmaceuticals Co. Ltd., Fortress Biotech, Inc., HDL Therapeutics Inc., HeartFlow Inc., Hummingbird Bioscience, Insmed Inc., Ionis Pharmaceuticals, IQVIA Inc., JanOne Biotech Holdings Inc., Janssen and Affiliates, Kaneka, Kowa Research Institute, Inc., Kyushu University, Lexicon Pharmaceuticals, Inc., LSG Kyushu University, Medimmune Ltd.,

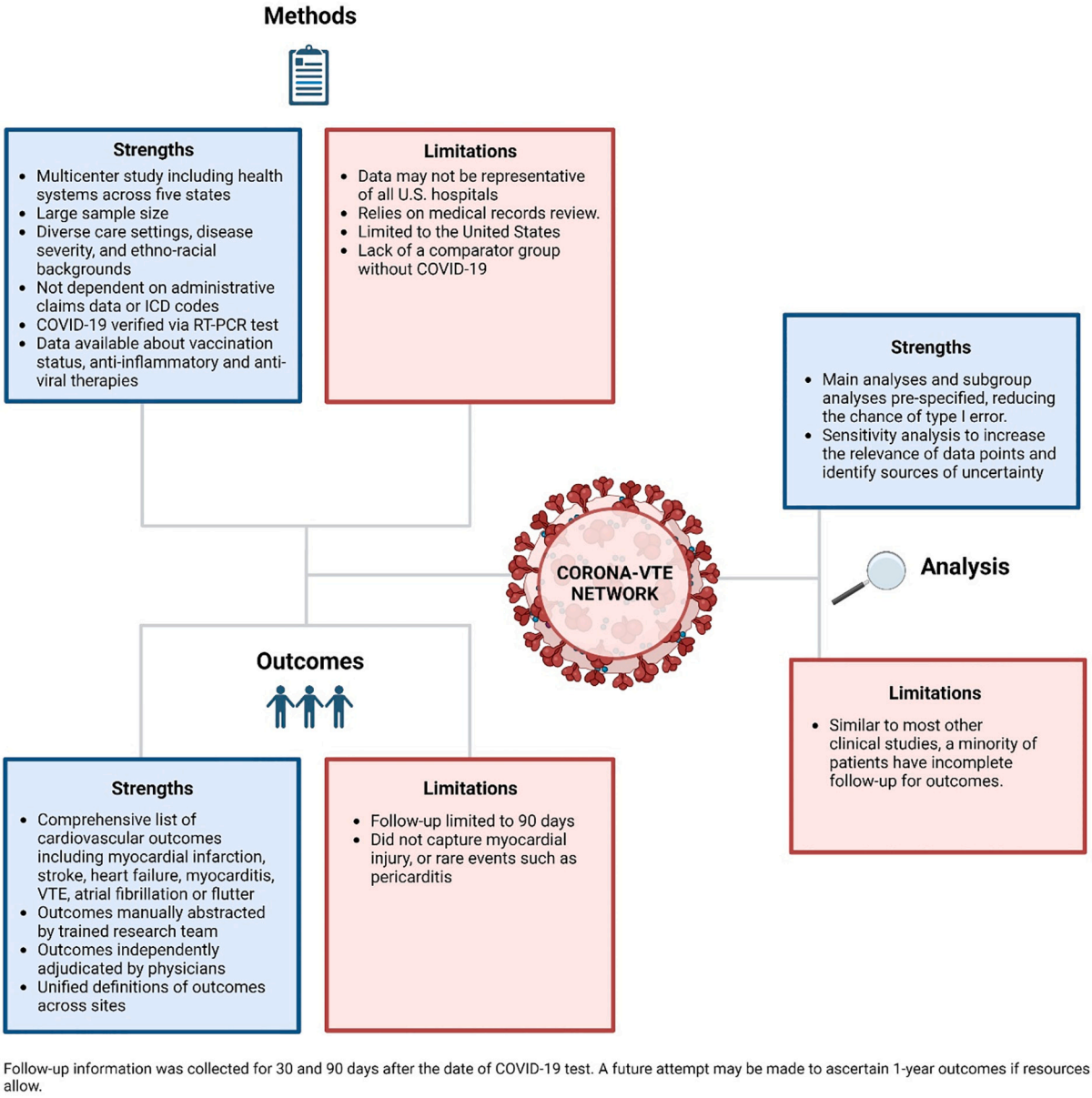

Fig. 3. Strengths and limitations of CORONA-VTE-Network compared with other studies. COVID-19 = Coronavirus disease 2019; RT-PCR = reverse transcription polymerase chain reaction; VTE = venous thromboembolism.

Medpace, Merck & Affiliates, Novartis Pharmaceuticals Corp., Novate Medical, Ltd., Novo Nordisk, Inc., Pan Industry Group, Pfizer Inc., PhaseBio Pharmaceuticals, Inc., PPD Development, LP, Prairie Education and Research Cooperative, Prothena Biosciences Limited, Regeneron Pharmaceuticals, Inc., Regio Biosciences, Inc., Rexgenero, Sanifit Therapeutics S.A., Sanofi-Aventis Groupe, Silence Therapeutics PLC, Smith & Nephew plc, Stealth BioTherapeutics Inc., State of Colorado CCPD Grant, The Brigham & Women's Hospital, Inc., The Feinstein Institutes for Medical Research, Thrombosis Research Institute, University of Colorado, University of Pittsburgh, VarmX, Virta Health Corporation, WCT Atlas, Worldwide Clinical Trials Inc., WraSer, LLC, and Yale Cardiovascular Research Group. Dr. Hsia also reports owning AstraZeneca stock. Dr. Bonaca receives support from the AHA SFRN under award numbers 18SFRN3390085 (BWH-DH SFRN Center) and 18SFRN33960262 (BWH-DH Clinical Project). Dr. Bonaca also reports stock in Medtronic and Pfizer. Dr. Sharma reports that he receives institutional grant funding from Boston Scientific Corporation and Vascular Medcure, is a board member for the Society for Vascular Medicine, and receives Speaking honoraria from Boston Scientific Corporation. Dr. Goldhaber reports research support from Bayer, BMS, Boston Scientific BTG EKOS, Janssen, NHLBI, and Pfizer, and consulting fees from Pfizer. Dr. Piazza has received research support from Bristol-Myers Squibb/Pfizer Alliance, Bayer, Janssen, Alexion, Amgen, Esperion, Boston Scientific Corporation and the NHLBI (1R01HL164717–01), and consulting/advisory fees from BMS, Boston Scientific Corporation, Janssen, PERC, NAMSA, Regeneron, Penumbra, and Amgen.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2023.05.019.

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