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

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Full Length Article

Intermediate versus standard-dose prophylactic anticoagulation and statin therapy versus placebo in critically-ill patients with COVID-19: Rationale and design of the INSPIRATION/INSPIRATION-S studies

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A B S T R A C T

Background: Microvascular and macrovascular thrombotic events are among the hallmarks of coronavirus disease 2019 (COVID-19). Furthermore, the exuberant immune response is considered an important driver of pulmonary and extra-pulmonary manifestations of COVID-19. The optimal management strategy to prevent thrombosis in critically-ill patients with COVID-19 remains unknown.
Methods: The Intermediate versus Standard-dose Prophylactic anticoagulation In cRitically-ill pATIents with COVID-19: An opeN label randomized controlled trial (INSPIRATION) and INSPIRATION-statin (INSPIRATION-S) studies test two independent hypotheses within a randomized controlled trial with 2 × 2 factorial design. Hospitalized critically-ill patients with reverse transcription polymerase chain reaction confirmed COVID-19 will be randomized to intermediate-dose versus standard dose prophylactic anticoagulation. The 600 patients undergoing this randomization will be screened and if meeting the eligibility criteria, will undergo an additional double-blind stratified randomization to atorvastatin 20 mg daily versus matching placebo. The primary endpoint, for both hypotheses will be tested for superiority and includes a composite of adjudicated acute arterial thrombosis, venous thromboembolism (VTE), use of extracorporeal membrane oxygenation, or all-cause death within 30 days from enrollment. Key secondary endpoints include all-cause mortality, adjudicated VTE, and ventilator-free days. Key safety endpoints include major bleeding according to the Bleeding Academic Research Consortium definition and severe thrombocytopenia (platelet count < 20,000/fL) for the anticoagulation hypothesis. In a prespecified secondary analysis for non-inferiority, the study will test for the non-inferiority of intermediate intensity versus standard dose anticoagulation for major bleeding, considering a non-inferiority margin of 1.8 based on odds ratio. Key safety endpoints for the statin hypothesis include rise in liver enzymes > 3 times upper normal limit and clinically-diagnosed myopathy. The primary analyses will be performed in the modified intention-to-treat population. Results will be tested in exploratory analyses across key subgroups and in the intention-to-treat and per-protocol cohorts.
Conclusions: INSPIRATION and INSPIRATON-S studies will help address clinically-relevant questions for antithrombotic therapy and thromboinflammatory therapy in critically-ill patients with COVID-19.

1. Introduction

Coronavirus disease-2019 (COVID-19) is an acute viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has caused a global pandemic, afflicting > 23.5 million patients worldwide and leading to > 810,000 deaths [1–5].

Although initially considered a respiratory illness, COVID-19 has multi-system manifestations [6]. Micro and macrothrombosis are among the hallmarks of the disease pathophysiology [7,8]. Acute illness, immobility, cytokine storm, platelet hyperreactivity [9], and direct viral thrombogenicity may predispose patients to a prothrombotic state [7]. Depending on whether the systematic screening is utilized,

Table 1
Inclusion and exclusion criteria.

Anticoagulation hypothesis	
Inclusion criteria	Exclusion criteria
• Adult patients (≥18 years), with RT-PCR-confirmed COVID-19admitted to ICU within 7 days of initial hospitalization, who do not have another firm indication for anticoagulation (such as mechanical valve, high-risk AF, VTE, or left ventricular thrombus),who are not enrolled in another blinded randomized trial, and are willing to participate in the study and provide informed consent. • Estimated survival of at least 24 h at the discretion of enrolling physician	• Weight < 40Kg • Use of systemic anticoagulation for another indication (mechanical valve, ECMO, AF, left ventricular thrombus, or diagnosed VTE) • Overt bleeding at the day of enrollment • Known major bleeding within 30 days (according to the Bleeding Academic Research Consortium (BARC) definition, Appendix A) • Platelet count < 50,000/Fl • Pregnancy (as confirmed by beta-HCG testing among female patients < 50 years) • History of heparin induced thrombocytopenia or immune thrombocytopenia • Ischemic stroke within the past 2 weeks • Major head or spinal trauma in the past 30 days • Craniotomy/major neurosurgery within the past 3 months • Known brain metastases or vascular malformations (aneurysm) • Presence of an epidural, spinal or pericardial catheter • Major surgery other than neurosurgery within 14 days prior to enrollment • Coexistence of severe obesity (weight > 120Kg or BMI > 35Kg/M^2 along with severe renal insufficiency defined as CrCl < 30 mL/min) • Allergic reaction to study medications • Lack or withdrawal of informed consent
Statin hypothesis	
inclusion criteria	Exclusion criteria
• Patients enrolled for the anticoagulation randomization • Willingness to participation in the study and providing informed consent	• Baseline liver function tests > 6 times upper normal limits • Total creatine kinase > 500 U/L • Active liver disease (LFT > 3 times upper normal limit plus histologic finding including cirrhosis or inflammation or necrosis) • Routine use of statins prior to the index hospitalization • Previous documented statin intolerance

Beta-HCG: human chorionic gonadotropin, BMI: Body Mass Index, CrCl: Creatinine Clearance, CK: Creatine kinase, COVID 19: coronavirus disease 2019, ICU: intensive care unit, LFT: liver function test, RT-PCR: reverse transcriptase polymerase chain reaction (PCR), ULN: upper limit of normal, VTE: venous thromboembolism.

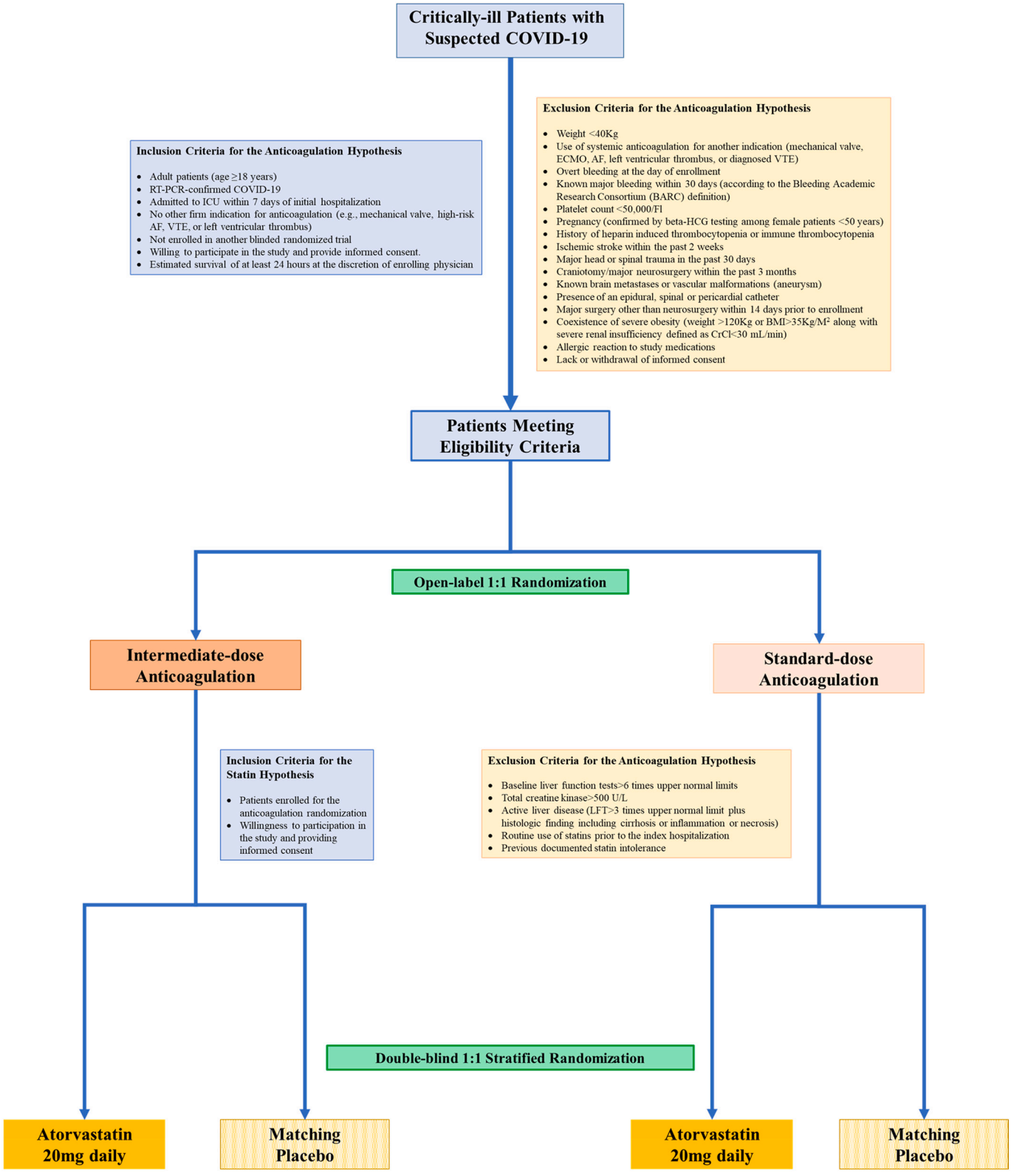


Fig. 1. Study flow diagram.

Table 2
Simplified dosing strategies for intermediate dose (intervention arm in first hypothesis) applied in study sites.

	Intermediate dose anticoagulation			Standard dose prophylaxis		
Weight (kg)	CrCl[1] > 30 mg/dL enoxaparin	15 < CrCl ≤ 30 mg/dL enoxaparin	CrCl ≤ 15 mg/dL UFH	CrCl[1] > 30 mg/dL enoxaparin	15 < CrCl ≤ 30 mg/dL enoxaparin	CrCl ≤ 15 mg/dL UFH
41–50	50 mg daily	40 mg daily	10,000 U SC BID	40 mg daily	30 mg daily	5000 U SC BID
51–60	60 mg daily	40 mg daily	10,000 U SC BID	40 mg daily	30 mg daily	5000 U SC BID
61–70	70 mg daily	40 mg daily	10,000 U SC BID	40 mg daily	30 mg daily	5000 U SC BID
71–80	80 mg daily	40 mg daily	10,000 U SC BID	40 mg daily	30 mg daily	5000 U SC BID
81–90	90 mg daily	50 mg daily	10,000 U SC BID	40 mg daily	30 mg daily	5000 U SC BID
91–100	100 mg daily	50 mg daily	10,000 U SC BID	40 mg daily	30 mg daily	5000 U SC BID
101–110	110 mg daily	60 mg daily	10,000 U SC BID	40 mg daily	30 mg daily	5000 U SC BID
111–120	120 mg daily	Excluded*			Excluded*	
121–130	80 mg BID			40 mg BID		
131–140	90 mg BID			40 mg BID		
141–150	90 mg BID			40 mg BID		
151–160	100 mg BID			40 mg BID		
161–170	100 mg BID			40 mg BID		
171–180	110 mg BID			40 mg BID		

CrCl: creatitine clearance. Due to complexity of escalated dosing, and rarity of the coexistence of severe renal insufficiency (CrCl ≤30 mg/dL) and severe obesity (weight > 120Kg) in the enrolling centers, the setting committee made an a priori decision to exclude these patients from enrollment.

Table 3
Study endpoint definitions.

Endpoint	Definition
Deep venous thrombosis	Any deep vein thrombosis diagnosed in the upper (internal jugular, subclavian, axillary/brachial), or lower extremity (iliac, femoral/popliteal, gastrocnemius, peroneal, posterior tibial) or the inferior vena cava or deep splanchnic veins based on ultrasonography, or contrast-enhanced vascular imaging, including computed tomography or angiography; or vascular magnetic resonance imaging.
Pulmonary embolism	Any pulmonary embolism diagnosed on CT angiography, V/Q scan, invasive pulmonary angiography, echocardiography (thrombus visualized in the main pulmonary artery), or at autopsy.
Undergoing ECMO	Use of veno-venous or veno-arterial extracorporeal membrane oxygenation.
Type 1 myocardial infarction (T_1MI)	Rise and/or fall in cardiac troponin values with at least on value above the 99th percentile upper reference limits with at least one of the followings; symptoms of ischemia, or new or presumed new ischemic ECG change, or Development of pathologic Q waves on the ECG, or Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent ischemic etiology; confirmed by coronary angiography, intravascular imaging or autopsy.[a]
Ischemic stroke	An acute episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction and verified by dedicated brain imaging and confirmed by neurology consultation.
Hemorrhagic stroke	A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma and verified by dedicated brain imaging.
Acute limb ischemia	Sudden decrease in limb perfusion that threatens limb viability with confirmed arterial obstruction based on duplex ultrasonography or contrast-enhanced vascular imaging, including computed tomography or angiography; or vascular magnetic resonance imaging.
Ventilator free days	Difference between total number of days alive post-enrollment and total number of days on invasive mechanical ventilation
Atrial fibrillation	New incident atrial fibrillation identified on electrocardiogram, or telemetry monitoring
Renal replacement therapy	Undergoing venovenous hemofiltration, hemodialysis, or peritoneal dialysis in patients without prior history of dialysis
All-cause death	Death due to any causes within the first 30 days. Considering the inaccuracies with adjudication of the cause of death in critically-ill patients with COVID-19 in the absence of systematic autopsy, the steering committee made the decision not to adjudicate the cause of death.
ICU length of stay	Total number of days spent in the ICU
Discharge from ICU	Alive discharge from the ICU
Major bleeding	BARC 3 or 5 bleeding (3: decrease in the hemoglobin of > 3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; 5: fatal)
Clinically-relevant non-major bleeding	Clinically-significant bleeding that warranted attention from the medical personnel, but not fulfilling criteria for major bleeding
Severe thrombocytopenia	Incident thrombocytopenia with platelet count < 20,000/fL
Rise in liver enzyme	Acute rise in liver enzymes > 3 times the upper reference limit
Clinically diagnosed myopathy	New myopathy diagnosed by the treating clinicians based on clinical and laboratory findings.

All endpoints will be adjudicated by the clinical events committee, blinded to group assignment.
Abbreviations: BARC: Bleeding Academic Research Consortium, CT: computed tomography, ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit, V/Q: Ventilation perfusion.

[a] Due to frequent elevation of cardiac troponins in the setting of COVID-19 for reasons other than COVID-19, and prior reports for non-specific electrocardiographic changes in the setting of COVID-19, the Streeting committee decided to designate T_1MI only if presence of cardiac biomarker elevations, electrocardiographic abnormalities or even wall motion abnormalities were verified by coronary angiography, intravascular imaging, or autopsy.

the studied population (wards versus intensive care units) and the use of thromboprophylaxis, the reported incidence of thrombotic events in patients with COVID-19 varies widely [10–18]. Thrombotic events may occur in the venous or arterial circulations, although venous thromboembolism (VTE) constitutes the predominant thrombotic condition [14]. Post-mortem studies have confirmed deep vein thrombosis, as well as pulmonary micro and macrothrombosis in patients with severe COVID-19, as the unexpected cause of death in some instances [19,20] [21].

The optimal antithrombotic regimen during hospitalization in these patients remains unknown [8]. For hospitalized patients with COVID-19, the majority of participants in a multinational panel of experts [7], as well as the guidelines from the World Health Organization, the National Institute of Health and the American College of Chest Physicians [12,22,23] recommend standard-dose prophylactic anticoagulation. However, some studies have suggested that high risk of VTE may persist

despite the routine use of standard prophylactic anticoagulation. Consequently, some experts suggest prescribing higher doses or frequencies of antithrombotic therapy [13,14,24–26]. Some health systems have instituted higher doses of anticoagulation, aligned with retrospective analyses that suggested lower mortality associated with more intense anticoagulation [27,28]. However, limited trial data exist to inform clinical practice. This is especially important because more intense anticoagulation is associated with an increased risk of bleeding.

In addition, the exuberant inflammatory response is known to play a role in the pathophysiology of acute respiratory distress syndrome (ARDS) [29] and especially that of COVID-19 [30,31]. Animal studies have shown that the inhibition of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase could modify several underlying mechanisms implicated in the development of ARDS [32]. In the HARP-2 trial, simvastatin, compared with placebo, was safe but did not improve the survival in patients with ARDS [33]. Subsequent analyses indicated interesting hypothesis-generating information for the potential role of statins in mitigating the outcomes in patients with hyperinflammatory sub-phenotype of ARDS [34].

This manuscript summarizes the design features of the INtermediate versus Standard-dose Prophylactic anticoagulation In cRitically-ill pATIents with COVID-19: An opeN label randomized controlled trial (INSPIRATION) and INSPIRATION-statin (INSPIRATION-S) studies. In a 2 × 2 factorial design randomized controlled trial, we aim to investigate the safety and efficacy of two pharmacological regimens (intermediate-dose versus standard-dose anticoagulation; and statin therapy with atorvastatin 20 mg/daily versus matching placebo) on outcomes of critically-ill patients with COVID-19.

2. Methods

2.1. Trial design and study sites

INSPIRATION/INSPIRATION-S will be a multicenter 2 × 2 factorial design randomized controlled trial with allocation sequence concealment and blinded endpoint adjudication. The allocation ratio will be 1:1 for both the anticoagulation and the statin components. The first randomization (anticoagulation) is open-label, and the second randomization (use of atorvastatin) is placebo-controlled and double blind. The study sites include 7 teaching hospitals in 2 cities in Iran (Tehran and Tabriz): Masih Daneshvari Hospital, Hazrate Rasool-e Akram General Hospital, Modarres Hospital, Sina Hospital, Firoozgar General Hospital and *Imam* Khomeini Hospital (all in Tehran, Iran), and *Imam* Reza Hospital (in Tabriz, Iran). Iran is among the countries facing a second surge of COVID-19 and the chosen hospitals represent high-volume teaching referral centers. Study design, coordination and follow-up are performed with support from Rajaie Cardiovascular Medical and Research Center and Tehran Heart Center. Prior experience from Iran, as well as centers elsewhere in the world suggested that the disease wave in COVID-19 may shift fairly quickly, with practical challenges for patient recruitment and follow-up. Therefore, all attempts were made to design the study with rigor, but also as quickly as possible.

The study protocol was reviewed and approved by the institutional review board at Rajaie Cardiovascular Medical and Research Center, Tehran, Iran, and accepted by all other participating study sites. The study goals and interventions will be discussed with eligible subjects (or their healthcare proxies). For subjects agreeing to participate, written informed consent will be obtained. The trial oversight will be undertaken by the Data Safety and Monitoring Board comprised of clinicians and an independent statistician, not involved with the design or conduct of the trial. Patient enrollment began on July 29, 2020 and enrollment is anticipated to continue until November 2020. The trial has been registered in clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT04486508).

2.2. Inclusion and exclusion criteria

In brief, adult hospitalized critically-ill patients with reverse transcription polymerase chain reaction (RT-PCR)confirmed diagnosis of COVID-19 within 7 days before the index presentation who do not have a history of recent major bleeding, bleeding diathesis, or an existing indication for therapeutic anticoagulation and have and estimated survival of at least 24 h will be considered for inclusion for the anticoagulation hypothesis. Patients enrolled in the anticoagulation study will be considered for eligibility for the second randomization to atorvastatin versus placebo. Major exclusion criteria for the second randomization consist of baseline routine use of statins, severe liver disease, and prior history of statin intolerance. Details regarding the inclusion and exclusion criteria are summarized in Table 1 and the study flow diagram (Fig. 1).

2.3. Intervention(s) and comparator(s)

For the INSPIRATION hypothesis, the study intervention is intermediate-dose anticoagulation. The anticoagulant regimen will be modified according to weight/body mass index, and creatinine clearance. Enoxaparin will be the primary agent for anticoagulation, with unfractionated heparin reserved only for patients with creatinine clearance of ≤15 mL/min according to Cockcroft-Gault Formula. Standard-dose prophylaxis was defined as enoxaparin 40 mg/day, unless adjusted for obesity or creatinine clearance. Details about the dosing algorithm for each arm is summarized in Table 2. Intermediate dosing was chosen since it was thought by the steering committee to have the potential to confer benefit while mitigating the high risk of bleeding associated with higher doses of therapeutic anticoagulation [35]. This choice was also in line with group consensus of the Global COVID-19 Thrombosis Collaborative Group for research priorities [8].

For the INSPIRATION-S hypothesis, the study intervention is statin therapy with atorvastatin 20 mg once daily. Subjects will be randomized in a double-blind fashion to atorvastatin versus matching placebo. The dose of atorvastatin was chosen with consideration for concomitant antiviral therapies for COVID-19 that may significantly interact with higher intensities of statin therapy [36].

2.4. Screening and randomization

A site physician at each of the recruiting hospitals will evaluate daily the newly admitted patients to the intensive care units (ICU). Patients meeting the eligibility criteria, will be randomized with a web-based randomization scheme in permutated blocks of four. The allocation sequence will remain concealed.

The first randomization will occur for the anticoagulation hypothesis (intermediate dose versus standard dose anticoagulation). Afterwards, on the electronic web-based randomization system, subjects will be screened for second randomization (atorvastatin 20 mg daily versus matching placebo). If patients meet the eligibility criteria for the second randomization, they will be randomized for the second hypothesis (statin therapy) stratified by the anticoagulation arm (Fig. 1). The randomization schedule was generated by an independent biostatistician, not otherwise part of the study team.

2.5. Study endpoints

The primary endpoint used for both randomizations is a composite of adjudicated acute arterial thrombosis, VTE, undergoing extracorporeal membrane oxygenation (ECMO), or all-cause death within 30 days from enrollment. No systematic screening is planned for VTE, and testing will be at the discretion of the treating physicians. Only objectively-confirmed VTE events will be sent for blinded adjudication. All-cause mortality has been shown to be common in hospitalized patients with COVID-19 in Iran [37] and expected to be even more

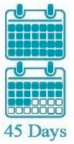
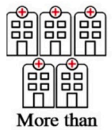
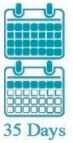
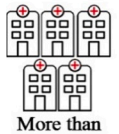
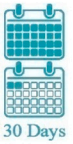
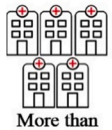
Trial Acronym & NCT	Narrative (summary of inclusion)	Setting (outpatient /inpatient/ ICU)	Intervention(s) comparator & number of participants	Primary Efficacy Endpoint	Main Safety endpoint	Follow up period for primary endpoint adjudication	Number of enrolling centers	Blinding Endpoint Adjudication
ACTIV-4 Outpatient NCT04498273	Adults with 40<age < 80 years and RT-PCR confirmed COVID-19 and elevated D-dimer and hsCRP who do not require hospitalization.		=7000 Aspirin 81mg/d Apixaban 2.5mgb.i.d Apixaban 5mgb.i.d Placebo	composite of cardiovascular and VTE related hospitalization s, symptomatic DVT, PE, arterial thromboembolism, MI, ischemic stroke, and all-cause mortality	Bleeding	 45 Days	 More than	Double Blind Blinded Endpoint Adjudication
PREVENT-HD NCT04508023	Adults with RT-PCR confirmed COVID-19 and at least one of the following (age>60 years, prior VTE, thrombophilia, CAD or PAD, stroke, cancer, diabetes, heart failure, BMI ≥35kg/m2, elevated D-dimer)		=4000 Rivaroxaban 10mg/d Placebo	Time to first occurrence of a composite of symptomatic VTE, MI, ischemic stroke, acute limb ischemia non-CNS systemic embolization, all-cause hospitalization, and all-cause mortality	ISTH major bleeding	 35 Days		Double Blind Blinded Endpoint Adjudication
NCT04483429	Adults with RT-PCR confirmed COVID-19 with at least 25% lung involvement on chest imaging and hypoxemia and elevated inflammatory markers		=268 Therapeutic dose (Enoxaparin/UFH in case of CrCl<40) for 7days then switch to prophylactic Prophylactic dose (Enoxaparin/UFH)	Rate of invasive mechanical ventilation	Death	 28 Days		Open Label Blinded Endpoint Adjudication
ACTIV-4 Inpatient NCT04505774	Adults (≥ 18 years) within 72 hours of hospital admittance or positive "COVID test"		=2000 Therapeutic dose (Enoxaparin/ UFH) Prophylactic dose (Enoxaparin/UFH)	Organ Support (respiratory or vasopressor) free Days	Major Bleeding (ISTH), HIT	 21 Days	 More than	Open Label Blinded Endpoint Adjudication
NCT04360824	Adults (≥18 years) with laboratory-confirmed COVID-19 and Modified ISTH Overt DIC score ≥ 3		=170 Intermediate dose (Enoxaparin) Prophylactic dose (Enoxaparin)	All-cause mortality	Major Bleeding (ISTH)	 30 Days		Open Label NA
ATTACC NCT04372589	Adults (≥18 years) p with microbiologically-confirmed COVID-19 enrolled < 72 hours of hospital admission or of COVID-19 confirmation		=3000 Therapeutic dose (tinzaparin/dalteparin/UFH) Prophylactic dose (Enoxaparin)	Freedom from invasive mechanical ventilation, all-cause mortality	Major Bleeding (ISTH)	 30 Days	 More than	Open Label NA

Fig. 2. Ongoing randomized trials on anticoagulant therapy in COVID-19.

Fig. 2. (continued)

Fig. 2. (*continued*)

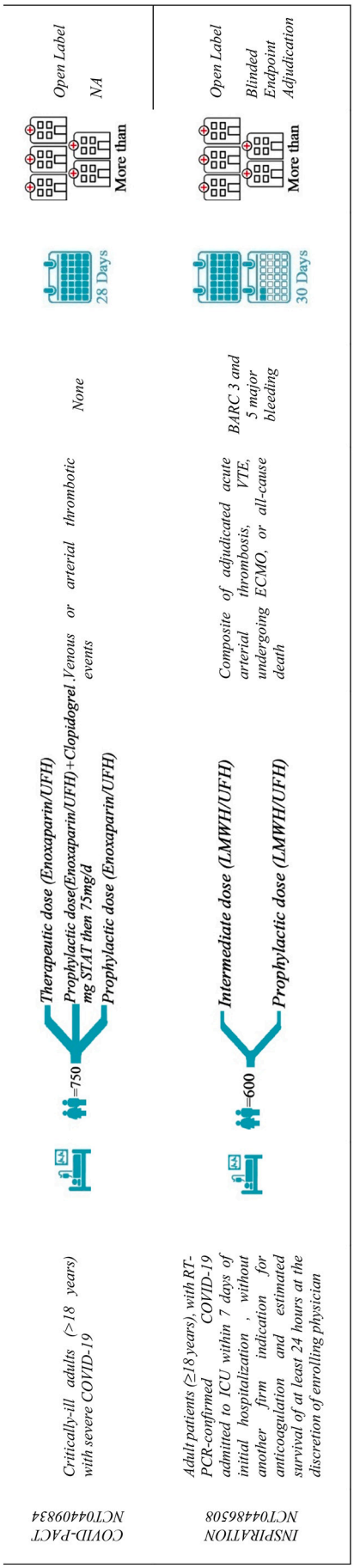


Fig. 2. (*continued*)

common among critically-ill patients. The decision to include ECMO in the primary endpoint was for robustness. Use of ECMO, albeit rare in the enrolling sites, indicates marked clinical deterioration. In addition, it necessitates (more than prophylactic) anticoagulation. For these reasons, the steering committee made an a priori decision to use it as a component of the primary endpoint (rather than an issue causing protocol non-adherence).

The main secondary efficacy endpoints include all-cause mortality, adjudicated VTE, and ventilator-free days. Key safety endpoints include major bleeding according to the Bleeding Academic Research Consortium definition [38], clinically-relevant non-major bleeding, and severe thrombocytopenia (platelet count < 20,000/fL) for the anticoagulation hypothesis. For the statin hypothesis, the main safety endpoints include rise in liver enzymes > 3 times upper normal limit, and clinically-diagnosed myopathy (Fig. 1). Study endpoints and their definitions are summarized in Table 3.

During the assessment of the design paper and while the trial has been ongoing, the study group received feedback for considering the assessment of functional status in patients who survived to hospital discharge. The steering committee decided to consider the inclusion of the Post-COVID-19 Functional Status (PCFS) scale [39] for post-discharge and 1-month follow-up interviews for the second half of the enrollment period.

All serious adverse events and clinical endpoints will be assessed and adjudicated by a centralized Clinical Events Committee which will meet online on a weekly basis and adjudicate the events, blinded to the treatment assignments.

2.6. Other data elements

Other data elements in the study include the demographics, comorbid conditions (including history of diabetes, hypertension, coronary or peripheral arterial disease, heart failure, and venous thrombosis). Prior use of statins and medications working on the renin-angiotensin-aldosterone system will be ascertained. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score will be calculated at the time of ICU admission. Laboratory tests of interest include baseline and nadir hemoglobin and platelet counts, as well as plasma creatinine values. In centers where digital electrocardiograms are available, an electrocardiogram will be recorded for future exploratory analyses. Key concomitant medical therapies including use and dose of corticosteroids, antiviral therapies, antiplatelet agents, ascorbic acid and colchicine, will be recorded.

2.7. Data abstraction and entry

During the course of ICU stay or de-escalation of care to medical wards, a dedicated site physician will continue to monitor each patient and extract the necessary data elements. In case of hospital discharge, regular weekly phone interviews will be performed until 30 days from enrollment or death, whichever that occurs first. If phone interview is indicative of a hospitalization or a serious adverse event, additional records will be requested. Data will be entered into standardized case report forms and subsequently entered into an online database. Periodic site visits will ensure appropriate screening and data entry into case report forms. Electronic data entry will be double-checked by a separate monitor.

2.8. Statistical analysis

Categorical variables will be reported as frequency counts (percentages and 95% confidence intervals). Continuous data will be summarized as mean and standard error of the mean, or median with 25/75 interquartile ranges (if not normally distributed).

The primary efficacy analyses will be performed in the modified intention-to-treat (mITT) cohort, consisting of patients without post-

randomization exclusion (e.g., due to withdrawal of consent) who received at least one dose of their assigned treatment. Sensitivity analyses will be performed in the pure ITT and per-protocol cohorts. The per-protocol cohort is defined as patients who received the assigned treatment until the end of the study or until reaching a component of the primary endpoint, whichever occurred earlier. The primary safety analyses will be performed among patients who received at least one dose of the study drugs, and will be repeated in the per-protocol cohort.

For assessment of both hypotheses, a test of interaction will be performed between anticoagulation regimen and statin therapy with the primary outcome. If the test of interaction is negative ($P < 0.05$), the two hypotheses will be tested independently.

A two-sided alpha of 0.05 will be considered for both study hypotheses. Sample size estimates are based on the z approximation formula for the comparison of proportions between two different groups. For the anticoagulation hypothesis, based on the estimates from site investigators in the enrolling centers, the primary endpoint event rate for the standard dose group was estimated at 55%. Considering an absolute risk reduction of 12% in the primary endpoint in the intermediate dose group, the study will need a total of 544 patients to have 80% power to detect a significant difference between the two study groups. Considering that there may be a 10% dropout rate (for example due to withdrawal of consent, or no use of the study drugs), we decide to enroll 600 patients for the anticoagulation hypothesis. In addition, a prespecified secondary analysis for non-inferiority will be performed for major bleeding in patients receiving intermediate-dose versus standard dose pharmacological prophylaxis. Considering event rates of 5.5% and 6.5% in standard dose and intermediate dose anticoagulation arms respectively for major bleeding [35,40], and a non-inferiority margin of 1.8 as odds ratio, the study would have 80% power to detect the non-inferiority of intermediate-dose anticoagulation. Pre-specified analyses will be performed based on sex, age, weight, history of hypertension, the APACHE II score, and baseline D-dimer.

For the statin hypothesis, the sample size is estimated to be 30% less than the original sample size of the anticoagulation hypothesis. This will be due to systematic exclusion of patients who were on statins at baseline or those who meet other exclusion criteria for the statin randomization (Table 1). As such, considering 600 patients for enrollment in the anticoagulation hypothesis will yield 420 patients for the statin hypothesis. With a control arm event rate of 55% and an estimated relative risk reduction of 25% with statin therapy for the primary endpoint, the study will have 69% power to detect a significant difference for the statin hypothesis. At the determination of the steering committee, if patient enrollment is found to be continually feasible with respect to the disease wave and logistics at enrolling centers, it has been specified a priori that enrollment could be extended, with no interim efficacy analyses, until the second randomization has 80% power to detect a significant difference for the primary endpoint. For this purpose, 124 additional patients would need to be recruited for the statin randomization.

In accord with guidelines from the European Medicine Agency (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-adjustment-baseline-covariates-clinical-trials_en.pdf) and given that no other completed randomized trials for antithrombotic therapy in COVID-19 are available to advise on baseline covariates, we decided to use unadjusted models for the primary analysis for the anticoagulation hypothesis. In turn, for the statin hypothesis, the primary analysis will be adjusted for the stratification variable (i.e., anticoagulation arm). Since the event rates are assumed to accrue non-proportionally, Cox-proportional hazard models will not be used for primary analysis. Rather, logistic regression models with odds ratio as the effect measure will be used for primary analyses. However, Kaplan Meier plots will be used for graphical representation of the events in each arm considering the time to reaching the primary endpoint. Models will be repeated with Cox-proportional hazard models for sensitivity analysis. Statistical analyses will be performed via R statistical software package (R Core Team, Vienna, Austria).

2.9. Study oversight

The safety oversight will be under the direction of the Data and Safety Monitoring Board (DSMB) whose members are not part of the authors group. The DSMB members have full access to the study data, with help from an independent statistician, as well as all the reports by the Clinical Events Committee.

To provide the most informative results, without risking the possibility of an overinflated estimate of the effect size, the steering committee decided not to set pre-specified criteria for early termination for efficacy [41]. Similarly, the steering committee specified not to stop the trial prematurely for futility, unless further recruitment seemed unfeasible due a change in the disease wave or logistical limitations at enrolling centers, in which case the DSMB will make a determination of futility based on conditional probability.

With respect to stopping considerations for harm, the DSMB will perform analyses after recruitment of 25%, 50%, and 75% of the target population to indicate whether a significant increase in the primary composite endpoint or in all-cause mortality for intermediate-dose anticoagulation arm has occurred, compared with the standard-dose prophylaxis arm with a P-value threshold of 0.01. Bleeding events may become more frequent with intermediate-dose anticoagulation compared with standard-dose anticoagulation. To consider early stopping for harm, an absolute 10% excess in bleeding events, with two-sided P-value of 0.016 (0.05 divided by 3, the number of interim analyses) will be required. Early termination for harm will be contingent on the absence of a counterbalancing efficacy improvement at the discretion of the DSMB. Criteria for early stopping due to harm for the anticoagulation randomization and for statin randomization also include an excess in the primary endpoint or all-cause mortality, with a P-value threshold of 0.01. The DSMB will communicate safety concerns or other oversight issues with the study principal investigators (PS and BB).

3. Discussion

This manuscript summarizes the methodological features of the INSPIRATION and INSPIRATION-S studies. With the increasing medical and economic devastation of COVID-19, it is imperative to identify safe and effective therapies to mitigate patient outcomes. Besides the promising results with dexamethasone [42] and remdesivir [43], no other therapies have shown benefits for patients with severe COVID-19.

The INSPIRATION study can further elucidate whether intermediate dose anticoagulation can confer benefit, primarily by reducing the thrombotic event rates, and thereby mortality. Several ongoing randomized trials are trying to address the potential utility of various intensities of antithrombotic agents for patients with COVID-19. Fig. 2 summarizes the list of randomized trials of anticoagulant therapy for COVID-19 registered at clinicaltrials.gov by August 14, 2020. These studies span a wide range of outpatient and inpatient illness severity for patients with COVID-19. The vast majority of these trials excludes patients who require therapeutic anticoagulation or those with high risk of bleeding, although the definition of the latter is variably defined across these trials.

In turn, the hypothesis tested in INSPIRATION-S will assess whether targeting thromboinflammatory pathways with atorvastatin has the potential to mitigate the clinical outcomes [44,45]. Results from several additional ongoing statin trials (Fig. 3) will be informative in this regard.

The database may also lend support to additional ancillary analyses from this cohort of prospectively enrolled patients. Such analyses may include studies to explore the association between baseline use of renin-angiotensin-aldosterone antagonists and outcomes, machine learning algorithms to identify electrocardiographic features predictive of adverse outcomes, or subgroup analyses based on disease severity (such as

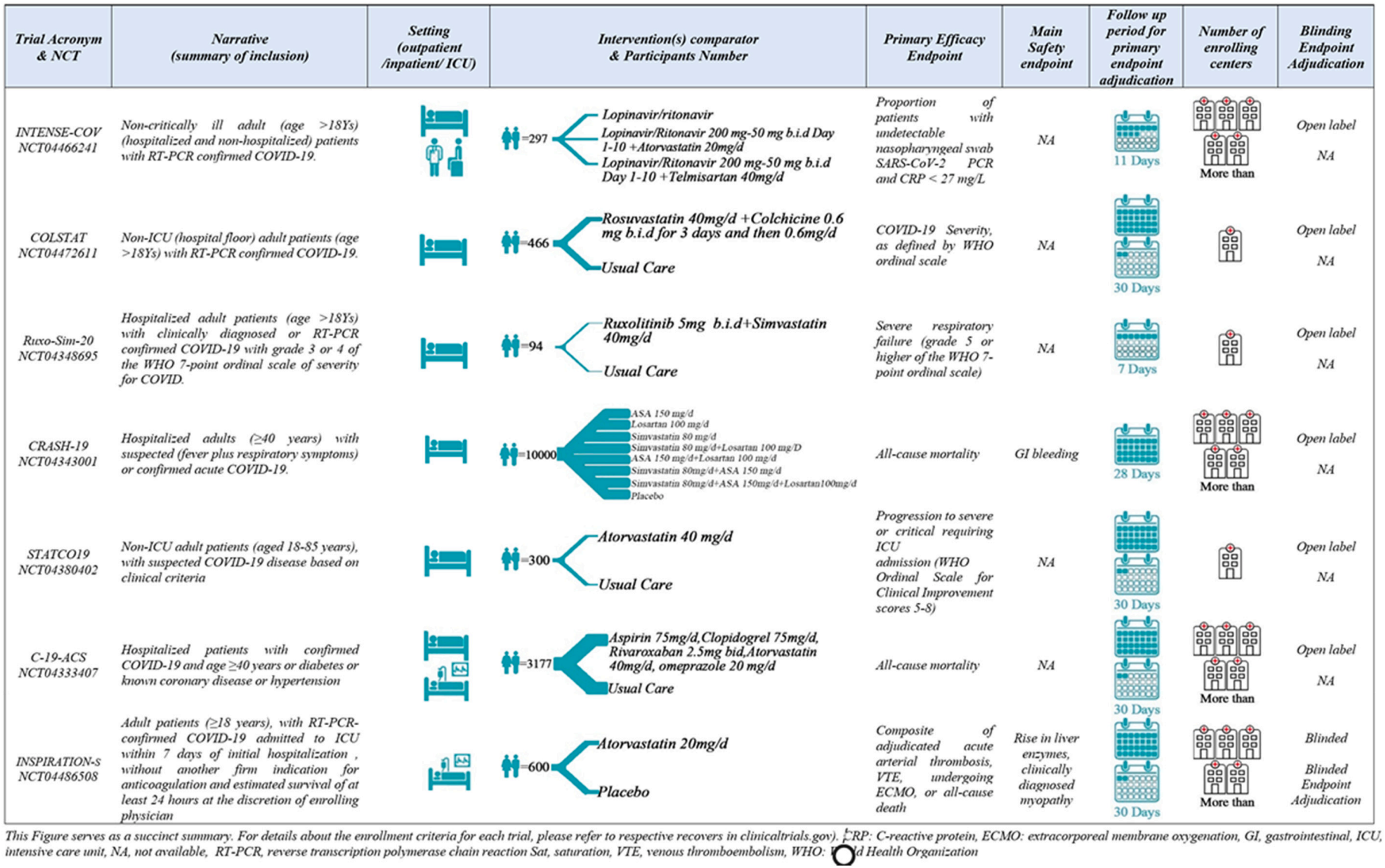


Fig. 3. Ongoing randomized trials at statin therapy in COVID-19.

the APACHE II score) on clinical outcomes.

Some design aspects of this randomized trial deserve further attention. Considering the unique situations caused by the COVID-19 pandemic, the study was designed in an extraordinarily short period of time, with time from inception of the idea to enrollment of the first patient in only 25 days. The pragmatic features of the study facilitated the timeliness of the process. In the face of the pandemic, most meetings, including those by the Clinical Events Committee, and those by the DSMB will be held online. Such approaches may also improve the efficiency of monitoring and communications.

Although INSPIRATION and INSPIRATION-S may help provide important information for management of patients with severe COVID-19, the limitations should be noted. First, due to time constraints and logistical challenges, it was not feasible to consider international patient recruitment. Second, the focus of both studies is on critically-ill patients with COVID-19. Therefore, generalizability will be limited to studies of critically-ill patients. Additional ongoing trials can determine the utility of other antithrombotic regimens among hospitalized patients with COVID-19 in medical wards, or among outpatients (Fig. 2). Third, INSPIRATION/INSPIRTION-S will be focusing on short-term (30-day outcomes). Although longer-term follow-up is desirable, the period of hospitalization and the early post-discharge phase are highest risk periods for the explored study endpoints. If additional funding and resources become available, we may expand the follow-up for up to 60 or 90 days. Finally, INSPIRATION will be an open-label pragmatic study. In depth discussions in the steering committee found it unfeasible to consider a double-blind double dummy design. Nevertheless, all outcomes will be adjudicated by the clinical events committee blinded to group assessment. The INSPIRATION-S study, in turn, will be double-blinded.

In conclusion, the INSPIRATION and INSPIRATION-S studies will help determine whether intermediate-dose anticoagulation or use of atorvastatin 20 mg daily can confer benefit in critically-ill patients with COVID-19. Preliminary results may be available before the end of 2020.

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Declaration of competing interest

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. Dr. Parikh reports being on the Advisory Board for Abbott, Boston Scientific, Medtronic, CSI, Philips, Janssen; Research Grants: Abbott, Boston Scientific, Surmodics, TriReme Medical, Shockwave Medical; and receiving Consulting fees from Terumo and Abiomed. Dr. Gupta received payment from the Arnold & Porter Law Firm for work related to the Sanofi clopidogrel litigation and from the Ben C. Martin Law Firm for work related to the Cook inferior vena cava filter litigation. Dr. Gupta holds equity in a healthcare telecardiology startup, Heartbeat Health, Inc. and received consulting fees from Edwards LifeSciences. Dr. Madhavan has received support from an institutional grant by the National Institutes of Health/National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center (T32 HL007854). Dr. Piazza has received research grant support to Brigham and Women's Hospital from EKOS, a BTG International Group company, Bayer, the Bristol Myers Squibb/Pfizer Alliance, Portola, and Janssen. He has received consulting fees from Amgen, Pfizer, Boston Scientific Corporation and Thrombolex. Dr. Kirtane reports Institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical. In addition to research grants, institutional funding includes fees paid to Columbia University and/or Cardiovascular Research Foundation for speaking engagements and/or consulting. Personal: Travel Expenses/Meals from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, CathWorks, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron. Dr. Lip reports consultant fees from Bayer/Janssen, BMS/Pfizer, Boehringer Ingelheim, Verseon and Daiichi-Sankyo and being a speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Dr. Krumholz reports personal fees from UnitedHealth, personal fees from IBM Watson Health, personal fees from Element Science, personal fees from Aetna, personal fees from Facebook, personal fees from Siegfried & Jensen Law Firm, personal fees from Arnold & Porter Law Firm, personal fees from Ben C. Martin Law Firm, personal fees from National Center for Cardiovascular Diseases, Beijing, ownership of HugoHealth, ownership of Refactor Health, contracts from the Centers for Medicare & Medicaid Services, grants from Medtronic and the Food and Drug Administration, grants from Medtronic and Johnson and Johnson, grants from Shenzhen Center for Health Information, and is a Venture Partner at FPrime. outside the submitted work. All other authors report no relevant Disclosures. Enoxaparin was provided through Alborz Darou, Pooyesh Darou and Caspian Pharmaceuticals companies, and atorvastatin and matching placebo was provided by Sobhan Darou. None of these companies were study sponsors and they had no other role and will not have a role in the design, conduct, analysis, or interpretation of the ongoing results or the decision to submit the resultant manuscript(s).

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