Intermediate *versus* Standard-dose Prophylactic anticoagulation In cRitically-ill pATIents with COVID-19 - An opeN label randomized controlled trial (INSPIRATION)

A Randomized Trial of Statin Therapy with Atorvastatin In Critically-ill patients with COVID-19: INSPIRATION-S

Investigators

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BACKGROUND

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 an unprecedented global pandemic, afflicting millions of patients worldwide(1-3), including in Iran, where there have been over 300,000 diagnosed cases and more than 16,000 casualties(4).

Although initially thought to be a respiratory illness, it has become clear that COVID-19 may frequently have multi-system manifestations(5), and micro and macrothrombosis are among the hallmarks of the disease pathophysiology(6, 7). Acute illness, immobility, cytokine storm, and direct viral thrombogenicity may predispose patients to a prothrombotic state(6). Depending on the screening methods, the studied population (wards versus intensive care units) and the use of thrombophylaxis, the incidence of thrombotic events in patients with COVID-19 varies across studies between 7 % to 85 %(8-15). Thrombotic evens may occur in the venous or arterial circulations, although venous thromboembolism (VTE) seems to be the dominant thrombotic condition(12). In fact, several post-mortem studies have confirmed pulmonary micro and macrothrombosis in patients with severe COVID-19, as well as deep vein thrombosis as common occurrences, at times as the unexpected cause of death (16, 17).

Despite the perceived elevated risk of thrombosis, the optimal antithrombotic regimen in these patients remains unknown(7). For hospitalized patients with COVID-19, the majority of participants in a multinational panel of experts (6), as well as the guidelines from the World Health Organization and the National Institute of Health(18, 19) recommend standard-dose prophylactic anticoagulation. However, some studies have suggested high rates of VTE, despite the routine use of standard prophylactic anticoagulation and consequently suggest routine use of higher intensities of antithrombotic therapy(11, 12, 20), with some centers instituting higher doses of anticoagulation, aligned with retrospective analyses that suggested lower mortality associated with more intense anticoagulation(21). Limited high-quality data exist to inform clinical practice.

In addition, exuberant inflammatory response is known to play a role in the pathophysiology of acute respiratory distress syndrome (ARDS)(22) and especially that of COVID-19(23, 24).Animal studies showed that the inhibition of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase could modify several underlying mechanisms that are involved in the development of acute respiratory distress syndrome (ARDS)(25). In the

HARP-2 trial, simvastatin, compared with placebo, was safe but did not improve the survival in patients with ARDS (26), 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 (27).

In a 2x2 factorial design randomized controlled trial, we aim to investigate the safety and efficacy of two pharmacological regimens on outcomes of critically-ill patients with COVID-19. The first randomization entails open-label assignment to intermediate versus standard dose prophylactic anticoagulation. We hypothesize that intermediate dose compared with standard prophylactic dose anticoagulation will have a superior efficacy with respect to a composite of adjudicated acute arterial thrombosis, VTE, undergoing ECMO, or all-cause death at 30 days from enrollment. The second randomization will be double-blind assignment of the included patients to atorvastatin 20mg daily versus matching placebo. The hypothesis is that statin therapy will reduce in the composite of adjudicated acute arterial thrombosis, VTE, undergoing ECMO, or all-cause death at 30 days from enrollment.

OBJECTIVES

Anticoagulation Randomization

- **Overall Goal:**
    - To determine the comparative efficacy and safety of intermediate dose vs standard prophylactic anticoagulation in critically-ill hospitalized patients with COVID-19.
- **Specific Goals:**
    - To compare the intermediate dose vs standard prophylactic anticoagulation in critically-ill hospitalized patients with COVID-19 toward the 30-day primary composite endpoints of adjudicated acute arterial thrombosis, VTE, undergoing ECMO, or all-cause death at 30 days from enrollment.
    - To compare the rates of BARC major bleeding and severe thrombocytopenia in the two groups.

Statin Randomization

- **Overall Goal:**

- To determine the comparative efficacy and safety of atorvastatin 20 mg daily vs matching placebo in critically-ill hospitalized patients with COVID-19.

- **Specific Goals:**
  - To compare atorvastatin 20 mg daily vs matched placebo in critically-ill hospitalized patients with COVID-19 toward the 30-day primary composite endpoints of adjudicated acute arterial thrombosis, VTE, undergoing ECMO, or all-cause death at 30 days from enrollment.
  - To compare atorvastatin 20 mg daily vs matched placebo in critically-ill hospitalized patients with COVID-19 toward the rates of worsening liver function and clinically-diagnosed myopathy, as defined further below.

DESIGN

- 1:1 multicenter open-label 2x2 factorial design randomized controlled trial with allocation sequence concealment and blinded endpoint adjudication.

SETTING

- Nine teaching hospitals in Two cities (Tehran and Tabriz) in Iran will be involved:
  1. Rajaie Cardiovascular Medical and Research Center, Tehran, Iran
  2. Tehran Heart Center, Tehran, Iran
  3. Masih Daneshvari Hospital, Tehran, Iran
  4. Hazrate Rasool-e Akram General Hospital, Tehran, Iran
  5. Modarres Hospital, Tehran, Iran
  6. Sina Hospital, Tehran, Iran
  7. Imam Reza Hospital, Tabriz, Iran
  8. Firoozgar General Hospital, Tehran, Iran
  9. Imam Khomeini Hospital, Tehran, Iran

PARTICIPANTS

Critically-ill patients with reverse transcription polymerase chain reaction (RT-PCR) confirmed diagnosis of COVID-19 who meet the eligibility criteria. Patients included in the first randomization will be assessed for eligibility criteria and will be randomized in a stratified way (by anticoagulation treatment arm) for second randomization (statin versus placebo). Therefore, patients undergoing the second randomization would be a large subgroup of those in the first randomization.

Inclusion Criteria for Anticoagulation Hypothesis

- Adult patients (≥18 years), with PCR-confirmed COVID-19[1]admitted to ICU within 7 days of initial hospitalization[2], 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[3].
- Estimated survival of at least 24 hours at the discretion of enrolling physician

Exclusion Criteria for Anticoagulation Hypothesis

- 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

[1] COVID-19 will be defined by positive RT-PCR test plus either pulmonary infiltrates in radiography (chest X-ray or chest CT), and/or abnormal results for at least one of the following biomarkers: ESR, CRP, D-dimer, ferritin, LDH

[2] If patients are transferred across facilities, we will set time zero (for 7 days) as date of presentation to the first medical facility.

[3] For critically ill patients who are not able to participate in informed decision-making for participation in the study (e.g., due to sedation and mechanical ventilation), their healthcare proxy will be contacted for the possibility of enrollment and informed consent.

- 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

Inclusion Criteria for the Statin Randomization

- Patients enrolled for the anticoagulation randomization
- Willingness to participation in the study and providing informed consent

Exclusions Criteria for the Statin Randomization

- Baseline liver function tests>5 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

Patient screening process:

A site coordinator designated by the principal investigator of each recruiting center, will evaluate the newly admitted patients to the intensive care unit (ICU) in each center with respect to the trial eligibility criteria on a daily basis. After approval of the principal investigator of each center for meeting the eligibility criteria, the study will be discussed with candidate patients or their

healthcare proxies and if they agree and provide written informed consent, the patients will be randomized.

Randomization:

Permuted block randomization with two-set of block sizes of four via a web-based system will be used for the study. The first randomization will occur for the anticoagulation hypothesis.

Afterwards, on the electronic web-based randomization system, the patient will be screened for second randomization and if meeting the eligibility criteria, will be randomized for the second hypothesis (statin therapy) stratified by the anticoagulation arm (see the study flow diagram, below). The specifications for generation of the randomization schedule will be prepared by the study biostatistician and the steering committee. An independent biostatistician (from the steering committee), not otherwise part of the study team, will generate the randomization schedule. For this study, the randomization schedule refers to a list that includes the subject identification number, randomization block number, randomization code, and the allocated treatment.

INTERVENTION AND COMPARATOR:

In the present 2x2 factorial RCT, two intervention arms will be applied and each will have a separate comparator (see Figure 1 for details).

First hypothesis: Anticoagulation hypothesis.

INTERVENTION. Intermediate dose anticoagulation will be the tested regimen. The anticoagulation regimen will be modified according to weight/ body mass index, and creatinine clearance level (CrCl). 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.

COMPARATOR. Standard prophylaxis dose anticoagulation will be the anticoagulation of choice in the control arm. Enoxaparin will be the primary agent for anticoagulation, with unfractionated heparin reserved only for patients with creatinine clearance of ≤15 mL/min according Cockcroft-Gault Formula.

Second hypothesis: Statin hypothesis.

INTERVENTION. Atorvastatin ٢0 mg daily will be the statin therapy of choice in the intervention arm

COMPARATOR. Matching placebo will be used for the control arm

Table 1- INTERVENTION and COMPARATOR arms for the anticoagulation hypothesis

Intervention Arm	**Routine Protocol**
CrCl[1] ≥ 30 mL/min Enoxaparin 1mg/kg SC Daily[2]	CrCl ≥ 30 mL/min Enoxaparin 40 mg SC Daily
Obesity and CrCl ≥ 30 mL/min (weight≥120 kg or BMI≥35 kg/m^2) Enoxaparin 0.6 mg/kg SC twice daily (TBW)[2]	Obesity and CrCl ≥ 30 mL/min (weight≥120 kg or BMI≥35 kg/m^2) Enoxaparin 40 mg SC twice daily
15<CrCl<30 mL/min Enoxaparin 0.5 mg/kg SC Daily[2] (At least 40 mg)	15<CrCl<30 mL/min Enoxaparin 30 mg SC Daily
CrCl ≤15 mL/min UFH 10000 units SC twice daily	CrCl ≤15 mL/min UFH 5000 units SC twice daily

[1]Creatinine clearance will be calculated according to Cockcroft-Gault Formula. [2]Doses rounded up to nearest above 10 mg;

BMI, body mass index, CrCl, creatinine clearance, TBW, totally body weight, UFH, unfractionated heparin.

Please see the approximation tables for pragmatic dose assignment.

Table 2. Dosing strategies for Intermediate dose (Intervention arm in first hypothesis) applied in study sites

Weight (kg)	CrCl[1]>30 Enoxaparin	15< CrCl≤30 Enoxaparin	CrCl≤15 UFH
41-50	50 mg Daily	40mg Daily	10000 U SC Bid
51-60	60mg Daily	40mg Daily	10000 U SC Bid
61-70	70mg Daily	40mg Daily	10000 U SC Bid
71-80	80mg Daily	40mg Daily	10000 U SC Bid
81-90	90mg Daily	50mg Daily	10000 U SC Bid
91-100	100mg Daily	50mg Daily	10000 U SC Bid
101-110	110mg Daily	60mg Daily	10000 U SC Bid
111-120	120mg Daily	60mg Daily	10000 U SC Bid
121-130	80 mg Bid	Excluded	
131-140	90 mg Bid		
141-150	90 mg Bid		
151-160	100 mg Bid		
161-170	100 mg Bid		
171-180	110 mg Bid		

[1]Creatinine clearance will be calculated according to Cockcroft-Gault Formula (Weight: Total body weight).

CrCl, creatinine clearance, UFH, unfractionated heparin.

Table 3. Dosing strategies for standard dose anticoagulation (comparator arm in first hypothesis) applied in study sites

Weight (kg)	CrCl[1]>30 Enoxaparin	15< CrCl≤30 Enoxaparin	CrCl≤15 UFH
41-50	40mg Daily	30 mg Daily	5000 U SC Bid
51-60	40mg Daily	30 mg Daily	5000 U SC Bid
61-70	40mg Daily	30 mg Daily	5000 U SC Bid
71-80	40 mg Daily	30 mg Daily	5000 U SC Bid
81-90	40 mg Daily	30 mg Daily	5000 U SC Bid
91-100	40 mg Daily	30 mg Daily	5000 U SC Bid
101-110	40 mg Daily	30 mg Daily	5000 U SC Bid
111-120	40 mg Daily	30 mg Daily	5000 U SC Bid
121-130	40 mg Bid	Excluded	
131-140	40 mg Bid		
141-150	40 mg Bid		
151-160	40 mg Bid		
161-170	40 mg Bid		
171-180	40 mg Bid		

[1]Creatinine clearance will be calculated according to Cockcroft-Gault Formula (Weight: Total body weight).

CrCl, creatinine clearance, UFH, unfractionated heparin.

OUTCOMES

Primary endpoint

Composite of adjudicated acute arterial thrombosis[4] , venous thromboembolism[5] (VTE), undergoing ECMO, or all-cause death at 30 days from enrollment.

Secondary endpoints:

- All-cause mortality
- Objectively-confirmed VTE
- Ventilator free days: (Difference between days of ICU stay and days on invasive mechanical ventilation)

Exploratory Outcome:

- Objectively clinically-diagnosed type I acute myocardial infarction[6]
- Objectively clinically -diagnosed stroke
- Objectively clinically -diagnosed acute peripheral arterial thrombosis
- Median ICU length of stay (overall, and among survivors)
- Proportion of patients with alive discharge from ICU (either home or floor)
- Incident atrial fibrillation
- Undergoing new in-hospital renal replacement therapy (hemodialysis or venovenous hemofiltration or peritoneal dialysis)

Safety outcomes:

- Major bleeding according to the Bleeding Academic Research Consortium (BARC 3 or 5 bleeding)
- Clinically-relevant non-major bleeding (Clinically-significant bleeding, not fulfilling criteria for major bleeding)
- Severe thrombocytopenia (platelet count <20,000)
- Rise in liver enzymes, defined as increase liver function tests>3 times
- Clinically-diagnosed myopathy as assessed by clinical and biomarker tests according to the treating physicians.

[4] Acute arterial thrombosis is defined as any acute thrombosis in peripheral and visceral arterial system diagnosed by ultrasonography, computed tomography, magnetic resonance imaging, or arteriography.
[5] Acute venous thromboembolism composed of deep venous thrombosis, pulmonary emboli or both.
[6] As defined in the Universal Definition of Myocardial Infarction document

STUDY FLOW DIAGRAM

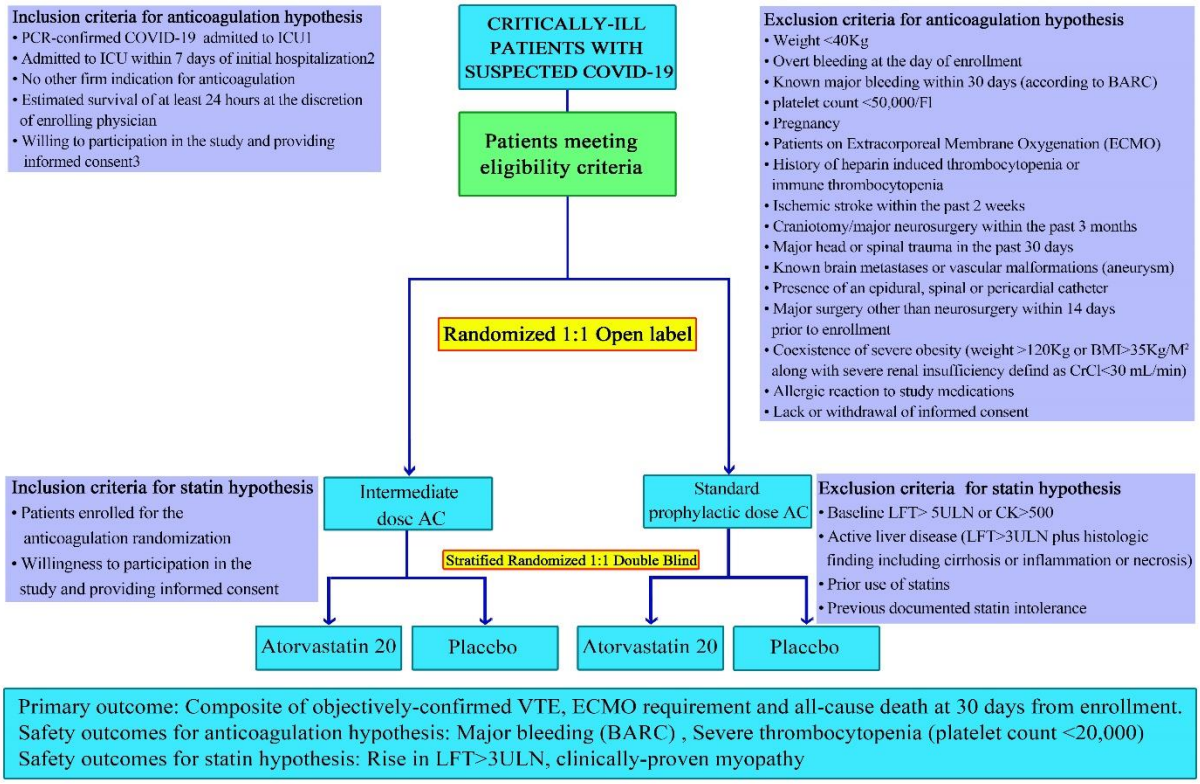

Figure 1. INSPIRATION and INSPIRATION-S study flow diagram. Allocation sequence will be concealed for both randomization sequences. For details about intermediate-dose and standard prophylactic dose anticoagulation, please refer to Table 1, 2 and 3.

AC, anticoagulation, BMI, Body Mass Index, CrCl, Creatinine Clearance, CK, Creatine kinase, COVID 19, coronavirus infection 19, ICU, intensive care unit, LFT, liver function test, PCR, polymerase chain reaction (PCR), ULN, upper limit of normal, VTE, venous thromboembolism

OTHER STUDY VARIABLES

Variable Name	Unit	Definitions
Baseline		
Age	Years	Years that has passed from the person's date of birth
gender	Male/Female	As reported in the medical records
weight	Kg	
Height	Cm	
BMI	Kg/m^2	
O2 saturation	%	As assessed by peripheral oximeter
temperature	^oC	Inner body temperature of person which has been calculated by oral thermometer
Blood pressure	mmHg	Systolic and Diastolic pressure of the fluid within blood vessels
Symptom onset	Day	Time from symptom onset to hospitalization
Hemoglobin	g/dl	
Platelet	$\times 10^3/ml$	
WBC	$Cells/mm^3$	
Lymphocyte count	$Cells/mm^3$	
BUN	mg/dl	
Cr	mg/dl	
Cardiac troponin	µg/lit	
CPK-MM	IU/L	
CPK (total)	IU/L	
ALT	IU/L	
AST	IU/L	
Alk P.	IU/L	
PT	Seconds	
INR	-	
PTT	Seconds	
D-dimer	ng/ml	Blood concentration of D-dimer
ESR	mm/h	The rate of sedimentation of erythrocytes in a tall thin tube of blood per hour
CRP	mg/L	Blood concentration of CRP
Anticoagulation regimen	Frequency	Type of anticoagulant drug and its dosage and route of administration
Statin regimen	Frequency	The arm of the study the patient has been assigned to statin or placebo (blindly reported as arm A vs arm B)
During the study		
Hb	g/dl	
Plt	$\times 10^3/ml$	
WBC	$Cells/mm^3$	
BUN	mg/dl	
Cr	mg/dl	
CrCl	mL/min	
PT	Seconds	

INR	-	
PTT	Seconds	
ESR	mm/h	
CRP	mg/L	
Lymphocyte count	Cells/mm^3	
Cardiac troponin	µg/lit	
CPK-MM	IU/L	
CPK (total)	IU/L	
ALT	IU/L	
AST	IU/L	
Alk P.	IU/L	
D-dimer	ng/ml	
By the end of 30 days or death		
Objectively proven DVT	Yes/No	Distal or proximal deep vein thrombosis which has been confirmed by ultrasonography or venography
DVT site	Lower distal DVT, Lower upper DVT, Upper DVT	Site of DVT
Objectively proven PE	Yes/No	Confirmed by at least one CTPA or lung scan
PE site	Sub-segmental/Segmental/Central	Site of PE
Suspected T1MI		Rise and/or fall in cardiac troponin values with at least on value above the 99th percentile URL ***and*** 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 T1MI		All the criteria in suspected MI ***and*** confirmed by coronary angiography, intravascular imaging or autopsy
Incident AF	Yes/No	Any AF episode which has been confirmed by at least one ECG or telemetry monitoring, in patients without prior history of AF
Objectively confirmed stroke	Yes/No	Any stroke episode which has been confirmed with appropriate diagnostic imaging (brain CT and/or brain MRI)
acute peripheral arterial thrombosis	Yes/No	Imaging confirmed acute peripheral arterial thrombosis (by ultrasonography, CT, MRI, or

		invasive angiography)
ICU length of stay	Days	Number of days that a patient has stayed in the ICU
ICU discharge status	Alive/Deceased	Status of patients regarding to mortality (alive/dead) at the time of discharge from ICU
Hospitalization length	Days	Total days of hospital stay
Hospital discharge status	Alive/Deceased	Status of patients regarding to mortality (alive/dead) at the time of discharge from ICU
Number of days on ventilator during hospitalization	Days	Number of days that a patient had been on ventilator during his/her hospitalization period
Respiratory support Type	Invasive mechanical ventilatory support Noninvasive mechanical ventilation (CPAP/BiPAP) High-flow nasal cannula Nonrebreather mask	Type of respiratory support during ICU stay
Vasopressor treatment	Day	Duration by which patients receive vasopressor treatment
Undergoing ECMO during hospitalization	Yes/No	
In-hospital mortality	Yes/No	Patient status regarding to being alive or dead at the end of hospital stay
Mortality	Yes/No	Patient status regarding to being alive or dead at the end of 30-day follow up
Major bleeding	Yes/No	Any major bleeding event regarding to BARC criteria
Need for renal replacement therapy	Yes/No	Use hemodialysis or veno-venous hemofiltration or peritoneal dialysis for a patient during the hospitalization period, due to acute kidney injury
thrombocytopenia	Yes/No	Platelet count < 150,000 /μL in a patient's blood
Severe thrombocytopenia	Yes/No	Platelet count < 20,000 /μL in a patient's blood
Liver impairment	Yes/No	Rise in ALT to 3 time greater than normal upper limit of normal
Myopathy	Yes/No	Rise in the serum level of muscle troponin, CPK-MM (and total CPK), LDH, and/or aldolase

STATISTICAL CONSIDRATIONS AND SAMPLE SIZE CALCULATION

Sample size is calculated for two main hypotheses separately. Statistical type I error (α) is considered at 0.05 in both calculations. Both the hypotheses are considered two sided. The primary analyses will be conducted in the modified intention- to-treat population (mITT) which consists of patients with assigned treatment who did not withdraw consent and received at least one dose of the study drugs.

For the anticoagulation hypothesis, based on the discussion with the enrolling centers, assuming the primary endpoint event rate for the standard dose group as 55% and an absolute risk reduction (ARR) of the primary endpoint in the intermediate dose group to be 12%, and alpha of 0.05, 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 (e.g. withdrawal of consent, or no use of the study drugs), we decide to enroll 600 patients for the anticoagulation hypothesis.

For the statin hypothesis, we anticipate the sample size to be 30% less than the original sample size of the anticoagulation hypothesis, due to systematic exclusion of patients who were on statins at baseline or those who meet other exclusion criteria for the statin randomization. Considering this limitation, with a sample size of 420 patients, a control arm event rate of 55% and an estimated relative risk reduction (RRR) of 25% with statin therapy for the primary endpoint, the study will have 69% power to detect a significant difference for the statin hypothesis. If patient enrollment is continually feasible at the discretion of the site investigators and the principal investigators, it has been *a priori* specified that enrollment could be extended, blinded to the results of the outcomes, until the second randomization has 80% power to detect a significant difference for the primary endpoint. For this purpose, 124 additional patients may be needed to recruited. The calculations are based on the z approximation formula for the comparison of proportions between two different groups.

In addition to mITT analysis as the primary analysis, simple ITT and per-protocol analyses will be performed as sensitivity analyses. The ITT cohort includes all patients with randomized assignment of treatments. Per-protocol analysis includes only those patients who completed the treatment as originally allocated until reaching the primary endpoint or the end of the study period, whichever that occurred earlier.

Categorical data are described as frequency counts and percentages. Quantitative data with normal distribution will be described via mean (standard error of the mean) in normally distributed or median (interquartile range) in the skewed interval variables. Ninety five percent confidence interval estimates will be reported for percentages for categorical variables. Comparisons between two groups will be performed via standard statistical tests, such as Pearson's chi squared (or Fisher's exact) test for nominal and independent sample t test (or its non-parametric equivalent, Mann Whitney U test).

For the primary analysis, treatment interaction between the two interventions will be tested in patients who are present for both randomizations. In the absence of significant interaction ($P<0.05$), each hypothesis will be tested independently. For the primary endpoint analysis for the anticoagulation hypothesis, it was decided to use unadjusted models for the primary analysis for the anticoagulation hypothesis. For the statin hypothesis, though, the primary endpoint analysis will be adjusted for the stratification variable (i.e., anticoagulation arm) according to recommendations by the European Medicines Agency (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-adjustment-baseline-covariates-clinical-trials_en.pdf). Since the event rates are assumed to accrue non-proportionally, Cox-proportional hazard model will not be used for primary analysis but will be used in a sensitivity analysis, that takes the time to events into consideration.

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(28, 29), along with odds ratio of 1.8 for non-inferiority margin, the study would have 79.5% power to detect the non-inferiority of intermediate anticoagulation. P values < 0.05 are considered as statistically significant for the primary endpoint analysis of each hypothesis. All other P-values will be considered as exploratory. Statistical analyses will be performed via R statistical software (R Core Team ,2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.URL https://www.R-project.org/).

Ethical consideration:

The study protocol along with patient informed consent will be approved by the Rajaie Cardiovascular Medical and Research Center(RHC) Ethics Committee, which is valid across all other participating hospitals. Each site PI will discuss the study goals, will explain about each investigational therapeutic strategy, and the potential risk and benefits of participating in the trial with the patient or their next of kin, in case patients are not conscious or able to make decisions. For those agreeing to participate, a written informed consent will be signed by the patients/their next of kin. During and after the trial, the researchers ensure that adequate medical care is provided to participants whenever any adverse event or complication associated with the trial occurs. In addition, any investigation-related complication related to the research will be communicated with the participants followed up and treated for free.

Registration

As part of the requirements for conducting randomized trials in Iran, the trial will be registered at Iranian Registry of Clinical Trials (www.irct.ir). In addition, the study will be registered at clinicaltrials.gov.

Serious Adverse events

Surveillance and reporting for the SAE will start immediately after enrollment and will continue until withdrawal of consent, death within the first 30 days, or the end of 30-day follow-up. SAEs will be assessed by data abstractors, and monitored and reported byeach site PI. All clinical AEs may be reported by the patients or directly being observed by the study physician. Upon reporting, sufficient documents should be collected by the site PI for presentation to the Clinical Events Committee (CEC) for adjudication. Post-baseline abnormal diagnostic imaging tests considered clinically relevant by the site PI must be recorded in the SAE page of the eCRF. Investigator should follow subjects with SAEs until the event has resolved or the condition has stabilized. The occurrence of SAE may come to the attention of study physician at daily visit during hospitalization. In case of hospital discharge prior to 30 days since randomization, SAE will be monitored by the study physician via phone call at 7-day intervals since randomization.

All SAE will be captured on the eCRF**.** AE will be reported on weekly basis by the site PI to CEC.

Serious adverse events include VTE, major bleeding, MI, severe thrombocytopenia, major bleeding (BARC 3 or BARC 5), MI, stroke, LFT abnormalities, myopathy, need for renal replacement therapy, need for ECMO, death.

VTE should be confirmed by a guideline-recommended imaging- modalities: venous doppler ultrasound for DVT and CTPA or V/Q scanning for pulmonary embolism. Escalation of care to venovenous or veno-arterial ECMO should be also registered as SAE. Bleeding complication will be assessed according to BARC criteria. For those meeting major bleeding criteria (BARC 3 or BARC5), the type of bleeding and need for transfusion will be further specified. New use of renal replacement therapy (either continuous venovenous hemofilration, or hemodialysis) will be reported as a serious adverse event. Liver failure will be evaluated with liver enzyme and an elevation of more than 3IU will considered as liver injuries. Clinically proven myopathy will also be recorded as AE.

Clinical Event Committee (CEC)

The members of CEC are listed in appendix B. CEC members will have an online meeting on a weekly basis. The meeting will be valid with at least >50% of members participating. The data will be de-identified, and the treatment arms will remain blinded when the data are being provided to the CEC. The de-identification process will be as follows: A separate username/password will be allocated for each CEC member, by which they will access to the electronic database. However, personal information and random allocation of each study participant will be hidden to the CEC members. De-identified imaging tests, laboratory values or surgical/interventional procedural reports will be presented as a proof of related events. The Committee will adjudicate the reported outcomes. The adjudicated data will be registered to the electronic database by a research nurse separate from recruiting centers. An official report regarding the assessed SAEs during each meeting, will be made at the end of each CEC meeting.

Data and Safety Monitoring Board (DSMB)

Safety oversight will be under the direction of the Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise (Appendix C), and not members of the steering committee or the authors group of the study and free from conflict of interest. The

DSMB will meet weekly to assess safety and efficacy data on each arm of the study. Each member of DSMB will have complete access (including personal information and random allocation of each participant) to the electronic database. Also the official weekly report of CEC will be provided to the DSMB members. The DSMB will provide its input to Rajaie Cardiovascular Medical and Research Center and the study PIs (PS and BB).
The studied interventions in this 2x2 factorial design trial have been available for clinical management of cardiovascular conditions for decades, with relatively known efficacy and adverse event profiles. Therefore, unlike new investigational therapies, the nature of adverse events are known and anticipated.

Trials that are prematurely stopped for efficacy may frequently have an overinflated estimate of the effect size. In order to provide the most informative results, the steering committee decided not to set pre-specified criteria for early termination for efficacy (30). Similarly, it was decided not to stop the study prematurely for futility, unless the second wave of the pandemic slows down during the recruitment, 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 consider stopping the study prematurely if interim analyses after 25%, 50%, or 75% recruitment indicate a significant increase in the primary composite endpoint or in all-cause mortality for intermediate-dose anticoagulation arm, compared with the standard-dose prophylaxis arm with a P-value threashold of 0.01. Bleeding events may become more frequent with intermediate-dose anticoagulation compared with standard-dose anticoagulation. In order to be considered for 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) be considered for early termination, contingent on the absence of a counterbalancing efficacy improvement at the discretion of the DSMB.

Interim analysis will be performed separately for each of the main study hypothesis (anti-coagulation and statin) when 25%, 50% and 75% of total data are obtained. For monitoring the efficacy and safety and preserving type I error throughout the study, an O-Brien-Fleming type alpha-spending function will be applied. The results will be assessed by DSMB and final decisions be made accordingly.

The relationship between an AE and the study products will be determined by the DSBM on the basis of its clinical judgment and the following definitions:

Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Possibly Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

Data collection and management responsibilities

Data collection is the responsibility of the study physician in each site under the supervision of the site PI. The site PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Appendix

Appendix A. Bleeding Academic Research Consortium (BARC) definition for Bleeding**(31)**

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

> ***Type 3a:*** Overt bleeding plus hemoglobin drop of 3 to 5 g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding
>
> ***Type 3b***: Overt bleeding plus hemoglobin drop 5 g/dL* (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) Bleeding requiring intravenous vasoactive agents
>
> ***Type 3c:*** Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision

Type 4: CABG-related bleeding Perioperative intracranial bleeding within 48 h Reoperation after closure of sternotomy for the purpose of controlling bleeding Transfusion of 5 U whole blood or packed red blood cells within a 48-h period† Chest tube output 2L within a 24-h period

Type 5: Fatal bleeding

> ***Type 5a:*** Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
>
> ***Type 5b:*** Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

**Corrected for transfusion (1 U packed red blood cells or 1 U whole blood1 g/dL hemoglobin).*

†Cell saver products are not counted.

Appendix B. Clinical Events Committee members:

1. Ahmad Amin, MD

2. Parham Sadeghipour, MD
3. Azita H. Talasaz, PharmD
4. Bahram Mohebbi, MD
5. Behnood Bikdeli, MD MS (ad-hoc member)

Appendix C- The Data and Safety Monitoring Board

1. Saeideh Mazloomzadeh, MD, PhD
2. Shiva Khaleghparast, PhD
3. Behshid Ghadrdoost, PhD
4. Mostafa Mousavizadeh, MD, MPH
5. Mohammad Reza Baay, MD

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