# STUDY PROTOCOL

## Public title

The effectiveness of atorvastatin for deep vein thrombosis prevention in cancer patients undergoing chemotherapy

## Scientific title

Comparing the effectiveness between the use of atorvastatin and rivaroxaban for deep vein thrombosis prophylaxis, inflammatory responses, and coagulation activities in cancer patients who have a high risk of thrombosis while undergoing chemotherapy: focus on IL-6, CRP, TF, F1+2, D-dimer, NF-KB, and TNF-alpha serum level and Doppler ultrasonography

## Indication

Thromboprophilaxis Deep Vein Thrombosis in Cancer Patients

## Coordinating Investigator

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## SYNOPSIS

### A. Introduction

The incidence of venous thromboembolism (VTE) in cancer patients is high which is even higher for those who receive chemotherapy. Most VTE events occur after chemotherapy has started; 18.1% in the first month, 47% in the first three months, and 72.5% in the first six months.

Venous thromboembolism is a major cause of death, morbidity, delays in treatment, and increased costs of care. The increased risk of death also occurs approximately threefold in asymptomatic deep vein thrombosis ( DVT).

Clinical studies have demonstrated the benefits and safety of VTE prophylaxis for medical patients, which support evidence-based recommendations for thromboprophylaxis in clinical practice.

Although VTE prophylaxis in cancer patients is recommended by the guidelines, the use of VTE prophylaxis by clinicians is limited. Most common reasons include cost considerations and concerns about bleeding complications. Several others include lack of knowledge or confidence about thromboprophylaxis guidelines, lack of vigilance, and reluctance to give daily injections for anticoagulant use as prophylaxis.

The immune system and inflammation play essential roles in the pathogenesis of cancer-associated VTE. Cancer and chemotherapy administration can cause inflammatory conditions, which trigger the NF-κB signaling pathway to produce pro-inflammatory cytokines. Pro-inflammatory cytokines such as CRP and IL-6 promote procoagulant status mainly by inducing TF expression. TF expression triggers the coagulation system characterized by increased levels of circulating thrombin and fibrin formation biomarkers such as F1+2 and D Dimer.

Statins have anti-inflammatory effects by decreasing proinflammatory cytokines and chemokines. Hence, statins can be possibly used as anti-thrombotic therapy with a lower risk of bleeding than anticoagulants, a lower price, and an easier way of administering them.

Research data on statins and VTE in cancer patients are sparse. A previous study was a prospective cohort showing the administration of statins and the low incidence of

VTE in cancer patients. The role of statins in preventing VTE in cancer patients requires confirmation in RCT studies.

Newman et al. analyzed data from 44 studies using Atorvastatin in 16,495 patients. Severe side effects are rare, and there have been no deaths from treatment with atorvastatin.

FXa plays a vital role in the coagulation cascade by activating intracellular signaling pathways via G-protein-coupled PARs that stimulate multiple intracellular signaling pathways of NF-κB and MAPK that induce inflammation and fibrotic responses. Rivaroxaban inhibits FXa and prothrombinase activity. Besides functioning as an anticoagulant, it also effectively inhibits the inflammatory process.

Rivaroxaban is an anticoagulant that is easy to administer by taking it orally every day. CASSINI study has demonstrated that thromboprophylaxis with Rivaroxaban during the intervention period has a lower incidence of thrombosis and lower bleeding side effects than placebo and does not require monitoring during therapy.

The results described above prompted a study to compare the effectiveness of atorvastatin and rivaroxaban for thromboprophylaxis. Other aims of this study are to prove the effect of atorvastatin administration on inflammatory response and coagulation activity and the incidence of DVT in cancer patients at high risk of thrombosis undergoing chemotherapy.

## B. Research Objectives

To compare the effectiveness of atorvastatin and rivaroxaban for DVT prevention in cancer patients with high risk of thrombosis undergoing chemotherapy.

## C. Benefits of Research Finding

To date, the guidelines for prophylaxis of DVT in cancer patients undergoing chemotherapy are anticoagulants. However, many clinicians have not adhered to these guidelines for several reasons, including cost considerations, concerns about the risk of bleeding, and a reluctance to give daily injections for prophylactic use of anticoagulant injections.

By knowing the effect of statins to reduce inflammatory biomarkers and activation of coagulation, which in turn can prevent the incidence of DVT in cancer patients undergoing chemotherapy, it is hoped that atorvastatin can be possibly as prophylactic therapy for DVT in cancer patients undergoing chemotherapy at a lower cost, low bleeding risk, and easier to use in giving.

## D. Hypothesis

1. Atorvastatin 20 mg administration for 3 months can be used as an alternative for thrombo-prophylaxis in cancer patients who have a high risk of thrombosis while undergoing chemotherapy
2. Atorvastatin 20 mg is as effective as rivaroxaban and has better cost-effectiveness for thrombo-prophylaxis in cancer patients who have a high risk of thrombosis while undergoing chemotherapy
3. Atorvastatin 20 mg administration for 3 months is not inferior compared to rivaroxaban as a thrombo-prophylaxis in cancer patients who have a high risk of thrombosis while undergoing chemotherapy
4. Atorvastatin 20 mg administration for 3 months will reduce the IL-6, CRP, TF, F1+2, D-dimer,NF-kB, and TNF-alpha serum level and reduce DVT incidence measured by Doppler ultrasonography

## E. Primary outcome measure

Deep vein thrombosis event measured using Doppler ultrasonography at baseline and 3 months

## F. Secondary outcome measures

1. IL-6 is measured using ELISA at baseline and 3 months
2. NF-kB is measured using ELISA at baseline and 3 months
3. CRP is measured using a spectrophotometer at baseline and 3 months
4. TF is measured using ELISA at baseline and 3 months
5. F1+2 is measured using ELISA at baseline and 3 months
6. D-dimer is measured using ELISA at baseline and 3 months

7. TNF-alpha is measured using ELISA at baseline and 3 months
8. Cost effectiveness is measured using the total cost for each subject

## G. Methods

The research was conducted at dr. Kariadi Hospital, Semarang, from January 2021 to December 2021. The research design is an randomized control trial with a double-blinding randomized pre-test-post-test control group design, to compare the effectiveness and cost-effectiveness of atorvastatin versus rivaroxaban as thromboprophylaxis and also to prove the effect of atorvastatin administration on inflammatory response, coagulation activity and the incidence of TVD in cancer patients at high risk of thrombosis (Korana risk score 2) undergoing chemotherapy.

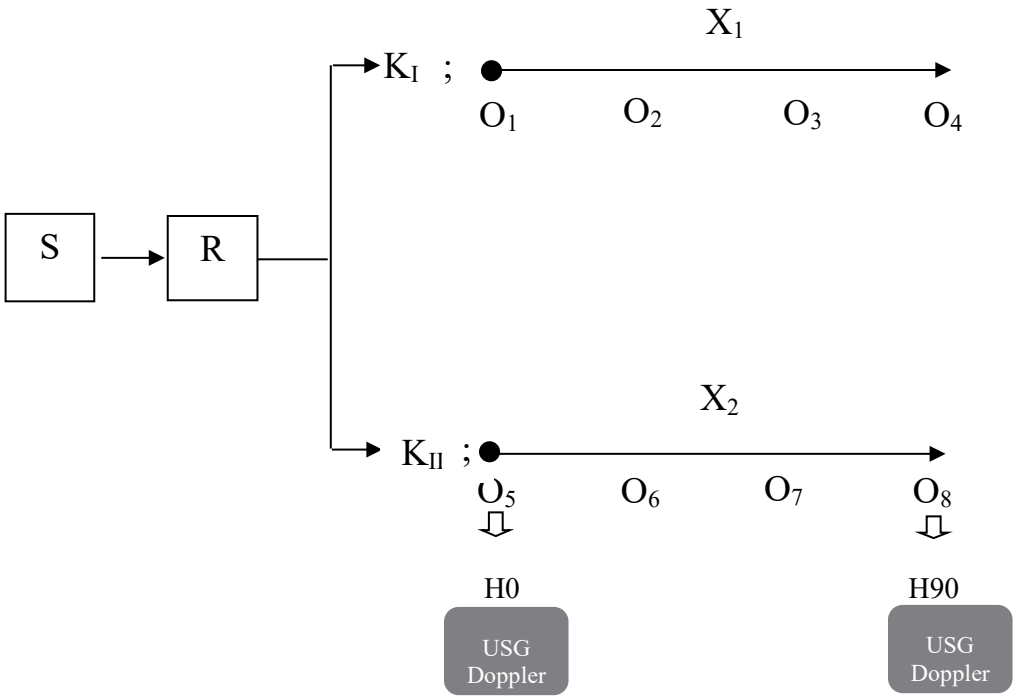


Figure 1. Research design

Information :

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|---|---|
| S | : Research subject |
| R | : Randomization |
| $K_I$ | : The treatment group is given Atorvastatin 20 mg/24 hours |
| $K_{II}$ | : Control group with Rivaroxaban 10 mg/24 hours |
| $X_1$ | : Intervention with Atorvastatin 20 mg/24 hours |
| $X_2$ | : Intervention with Rivaroxaban 10 mg/24 hours |

$O_1;O_5$ : Measurement of levels of IL-6, CRP, TF, F1+2, D Dimer, NFKB, TNF alpha and USG Doppler before treatment (day 0)

$O_4;O_8$ : Measurement of levels of IL-6, CRP, TF, F1+2, D Dimer, NFKB, TNF alpha and USG Doppler after treatment (day 90)

$O_2;O_6$ : Measurement of levels of IL-6, CRP, TF, F1+2, D Dimer, NFKB, TNF alpha and Well's score day 30

$O_3;O_7$ : Measurement of levels of IL-6, CRP, TF, F1+2, D Dimer, NFKB, TNF alpha and Well's score day 60

## H. Place and Time

This research was carried out at Dr Kariadi Hospital Semarang, planned to start in 2020-2021

## I. Population and sample

### 1. Population

The population reached in this study were all cancer patients with high risk of thrombosis who underwent chemotherapy at dr. Kariadi Semarang during the year 2020-2021.

### 2. Sample

The sample of this study were all cancer patients with high risk of thrombosis who underwent chemotherapy at dr. Kariadi Semarang who met the inclusion criteria and exclusion criteria.

Determination of the sample size using the sample size formula to test the hypothesis on 2 proportions. The minimum number of samples for each group is 40 research subjects, so a minimum total of 80 research subjects is required.

## J. Participant inclution criteria

1. Cancer patient with a definite diagnosis of cancer based on anatomy pathological examination

2. Cancer patients who have not received any chemotherapy
3. Khorana risk score ≥2
4. Age 18-60 years old
5. Has signed the participant agreement

**K. Participan exclution criteria**

1. Deep vein thrombosis diagnosed with Doppler ultrasonography examination at baseline
2. Within 14 days post-surgery
3. Pregnancy
4. Taking an anti-thrombotic drug
5. Congenital altered coagulation system
6. Creatinine clearance <30 ml/minute
7. Patients with AST level >3x upper normal limit
8. Patients with total bilirubin total >5 mg/dl
9. Patients with CK >3 x upper normal limit
10. Performance status ECOC ≥3
11. Patients with cardio-cerebrovascular disease
12. Patients with infection
13. Patients with active, major, serious, life-threatening bleeding that can not be overcome with medical or surgical intervention, esp in a critical area (intra-cranial, pericardial, retroperitoneal, intra-occular, intra-artikular, intraspinal)
14. Malignant hypertension
15. Congenital coagulopathy or severe platelet dysfunction
16. Severe and persistent thrombocytopenia (<20,000/µl)

## L. Ethics Approval

Approved 24/11/2020, Health Research Ethics Committee RSUP Dr. Kariadi Semarang (Sutomo St no. 16, Indonesia; +62 (0)24 8413476; kepk.rskariadi@gmail.com), ref: 665/EC/KEPK-RSDK/2020

## M. Identification and Classification of Research Variables

1. The independent variable is the administration of atorvastatin 20 mg/24 hours for 3 months
2. The administration of rivaroxaban as a control is the administration of Rivaroxaban 10 mg/24 hours for 3 months
3. The intermediate variable is the level of:
    a. NFKB
    b. IL-6
    c. CRP
    d. TNF alpha
    e. TF
    f. F1+2
    g. D Dimer
4. Confounding variables are::
    a. age
    b. gender
    c. cancer stage
    d. performance status
5. The dependent variable is::
    a. DVT incidence

## N. Operational definition

| No | Variable | Operational definition and measurement method | Scale | Unit |
|---|---|---|---|---|
| 1. | Administration of Atorvastatin | Administration of atorvastatin 20 mg/24 hours given 1 day after chemotherapy until the 90th day | Nominal | |
| 2. | Administration of Rivaroxaban | Administration of rivaroxaban 10 mg/24 hours given 1 day after chemotherapy until the 90th day | Nominal | |
| 3. | DVT high risk cancer patients | Cancer patient with a Khorana score ≥2 | Nominal | |
| 4. | Inflammatory response | It is the immune system's response to inflammation | | |
| | IL-6 | IL-6 is an inflammatory cytokine measured using the ELISA method with a kit (Human IL-6 Immunoassay Catalog Number HS600B) | Ratio | pg/ml |
| | CRP | CRP is an acute phase protein which was measured quantitatively by using a spectrophotometer method according to the principle of immuno-turbidy using the ADVIA 1800 auto analyzer. | Ratio | mg/l |
| | NFKB | NFKB is protein complex that controls transcription of DNA, cytokine production and cell survival | Ratio | pg/ml |
| | TNF- alpha | TNF alpha is an inflammatory cytokine produced by macrophages/monocytes during acute inflammation and is responsible for a diverse range of signalling events within cells, leading to necrosis or apoptosis | Ratio | pg/ml |

| | | | | |
|---|---|---|---|---|
| 4. | Coagulation activation | Coagulation activation is Is a process in the coagulation cascade with the end product fibrin which plays a role in blood clotting. | | |
| | TF | TF is the level of transmembrane glycoprotein which is the main initiator of coagulation measured by the ELISA method. | Ratio | pg/ml |
| | F1+2 | F1+2 Represents the level of prothrombin fragment that reflects the formation of thrombin measured by ELISA method examination | Ratio | µmol/l |
| | D Dimer | D Dimer is a product of fibrin degradation that increases in thrombosis as measured by the ELISA method | Ratio | mg/l |
| 5. | DVT incidence | On Doppler ultrasound, the diagnosis of TVD is indicated by the presence of a non-compressible deep vein segment | Nominal | |
| 6. | Age | Age is determined from research subject data based on the date of birth on the identity card | Ratio | Year |
| 7. | Gender | Gender is determined from the sex of the research subject | Nominal | |
| 8. | Blood Type | Classification of blood in humans based on the presence or absence of antigens in red blood cells and blood plasma. | Nominal | |
| 9. | Body Mass Index | The measure used to determine a person's nutritional status is obtained from the comparison of weight and height. | Ordinal | |
| 10. | Stage | Cancer stage is determined based on the criteria for each cancer | Ordinal | |

| | | | |
|---|---|---|---|
| 11. | Performance state | Performance status is the status of the patient's appearance that reflects the level of effectiveness of the patient and how far cancer has affected the patient.<br>Measured by the Eastern Cooperative Oncology Group (ECOG) performance status<br>0. Asymptomatic, fully active, able to perform all activities without hindrance.<br>1. Symptomatic but able to fully walk, limited physical activity and can do light or daily work.<br>2. Symptomatic, <50% in bed all day, able to walk and groom but unable to perform work activities.<br>3. Symptomatic, >50% in bed, >50% waking hours, limited self-care.<br>4. Totally paralyzed, unable to perform any self-care, completely in bed or chair.<br>0. 5. Die | Ordinal |
| 12. | Well's score | Well's score is a score that is used to predict the occurrence of DVT<br>*DVT likely* ≥ 2 point<br>DVT unlikely < 2 point | Ordinal |
| 13. | Khorana's score | Khorana score a score used to stratify the risk of TEV in patients with cancer (low, medium and high risk). Low risk<br>0<br>Intermediate risk 1-2<br>High risk ≥3 | Ordinal |
| 14. | Primary location of cancer | The location of the cancer site based on the type of cell of origin of the malignancy | Nominal |

| | | | |
|---|---|---|---|
| 16. | Chemotherapy regimen | Cytostatic drugs used in cancer treatment | Nominal |

**O. Procedure for giving intervention**

1. Atorvastatin 20 mg was given orally in the intervention group once a day. Researchers monitored the subjects' compliance in taking the drug every day.
2. Rivaroxaban 10 mg was given orally in the control group once a day. Researchers monitored the subjects' compliance in taking the drug every day.

**P. Method of collecting data and research samples**

1. Patients who met the research inclusion criteria were selected as prospective research subjects (screened for the presence of TVD with Doppler ultrasound of the lower limbs)
2. Before the research begins, the researcher explains to the research subjects about the research objectives, examination procedures and benefits to be obtained.
3. Research subjects who agree to conduct the study, are asked to prove their consent in writing by affixing a signature or thumbprint on the informed consent form as participants.
4. Initial interviews containing demographic data and other information about the subject were conducted at the beginning of the study. Then recorded clinical and laboratory data according to the basic research data sheet.
5. The research subjects were randomized in a double-blind manner where the researcher and research subjects did not know whether the respondent's status was included in the intervention or non-intervention group.

6. Prior to chemotherapy, venous blood was taken during working hours and inserted into a 10 mL EDTA tube. Venous blood was centrifuged to collect plasma and stored at minus 80◦C in the laboratory
7. The intervention group received chemotherapy and received atorvastatin tablets 20 mg/24 hours given up to 3 months after chemotherapy.
8. The control group underwent chemotherapy and received rivaroxaban 10 mg/24 hours which was administered up to 3 months after chemotherapy.
9. On the 7th day, a physical examination was performed to see signs of impaired liver function and signs of myopathy. Liver function laboratory tests (SGOT, SGPT) were performed to look for signs of impaired liver function. CK examination is done if there are signs of myopathy. If there is an increase in SGOT levels, SGPT 3 times the upper limit of normal and CK levels 3 times the upper limit of normal, the study is stopped (subsequent laboratory examinations every month).
10. Laboratory examination in the form of levels of IL-6, CRP, TF, F1+2 and D Dimer at the end of the 1st month (30th day), 2nd (60th day) and 3rd (day- 90), laboratory examinations are carried out within ±7 days from the specified time.
11. Monitor for signs of TVD by calculating the Well score, if the Well score is 2, a Doppler ultrasound is performed. At the end of the 1st month (30th day), the end of the 2nd month (60th day), the end of the 3rd month (90th day) a Doppler ultrasound examination was carried out, the Doppler ultrasound examination was carried out within ±7 days from specified time.
12. Monitor for signs of bleeding.
13. The results are recorded on the research form that has been provided.

14. After the number of research subjects or the end of the research deadline is completed, statistical analysis and research reports are carried out.

**Q. Methods of Measurement of Research Samples**

In this study, the levels of IL-6, CRP, TF, F1+2, NFKB and TNF alpha were examined in serum, while levels of D dimer were in plasma citrate. For these measurements, 9.5 mL of venous blood was taken, 5 mL was put into a vacutainer tube without anticoagulant and 4.5 mL was inserted into a vacutainer tube containing 0.5 mL of sodium citrate. Tubes without anticoagulant were centrifuged at 2500 g for 15 minutes, then serum was separated, coded and stored at -80oC until testing was performed.

IL-6 levels were checked by enzyme link immunosorbent assay (ELISA) using Elabscience Biotechnology reagents from the USA catalog number E-EL-H0102 96T. CRP levels were checked by ELISA using reagents from Sekisui Medical Co., LTD, Japan. The levels of TF, F1+2, NFKB and TNF alpha were examined with reagents from Elabscience Biotechnology USA with catalog numbers E-EL-H0040, E-EL-H1793, E-EL-H1386, E-EL-H0109, respectively. The results of the ELISA examination were read with an ELISA reader from Biotek, Vermont, USA at a wavelength of 450 nm. All samples were double-checked. If there is a value outside the linearity limit, then dilution is carried out and re-checked.

The blood in the citrate tube was also centrifuged at 2500 g for 15 min. Then the plasma was separated and the level of D dimer was examined by immunoturbidimetry using Innovance's reagent and the automated blood coagulation analyzer CS-2100i from Sysmex Corporation, Japan.

Doppler ultrasound was performed at the Radiology Department, dr. Kariadi Semarang. The equipment used is a Siemens ultrasound machine, Sonoline Omnia, serial number FBE 0322, model number GM-6801A2E00, made in Japan for Siemens Medical System, Inc. Ultrasonography Group, Issaquah, WA 98029-702 USA Part No. 5931030, distributed by Siemens Medical Systems, Issaquah, USA using linear multi-frequency 7.5 MHz transducers.

The examination is performed using an ultrasound probe to gently compress the vein. A non-compressible deep vein segment appearance is a sign of the diagnosis of TVD. Blood clots can be further described with real-time imaging such as Doppler duplex and color-flow (figure 2).

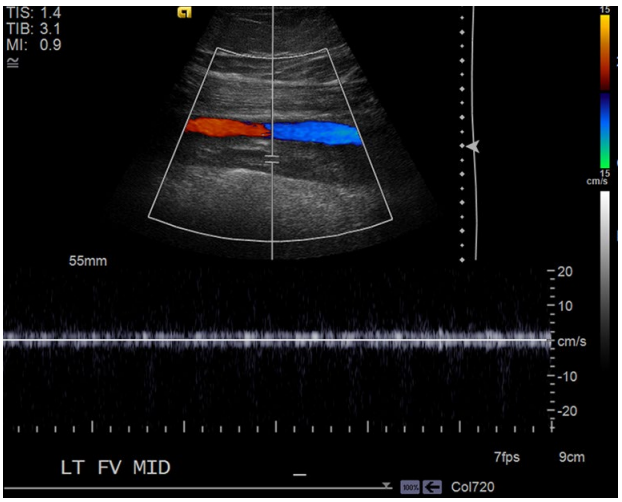


Figure 2. Venous color flow Doppler. Doppler ultrasound imaging of the left femoral vein showed complete occlusion by heterogeneous thrombus with dilated veins at the site of thrombosis.

**R. Research Flow**

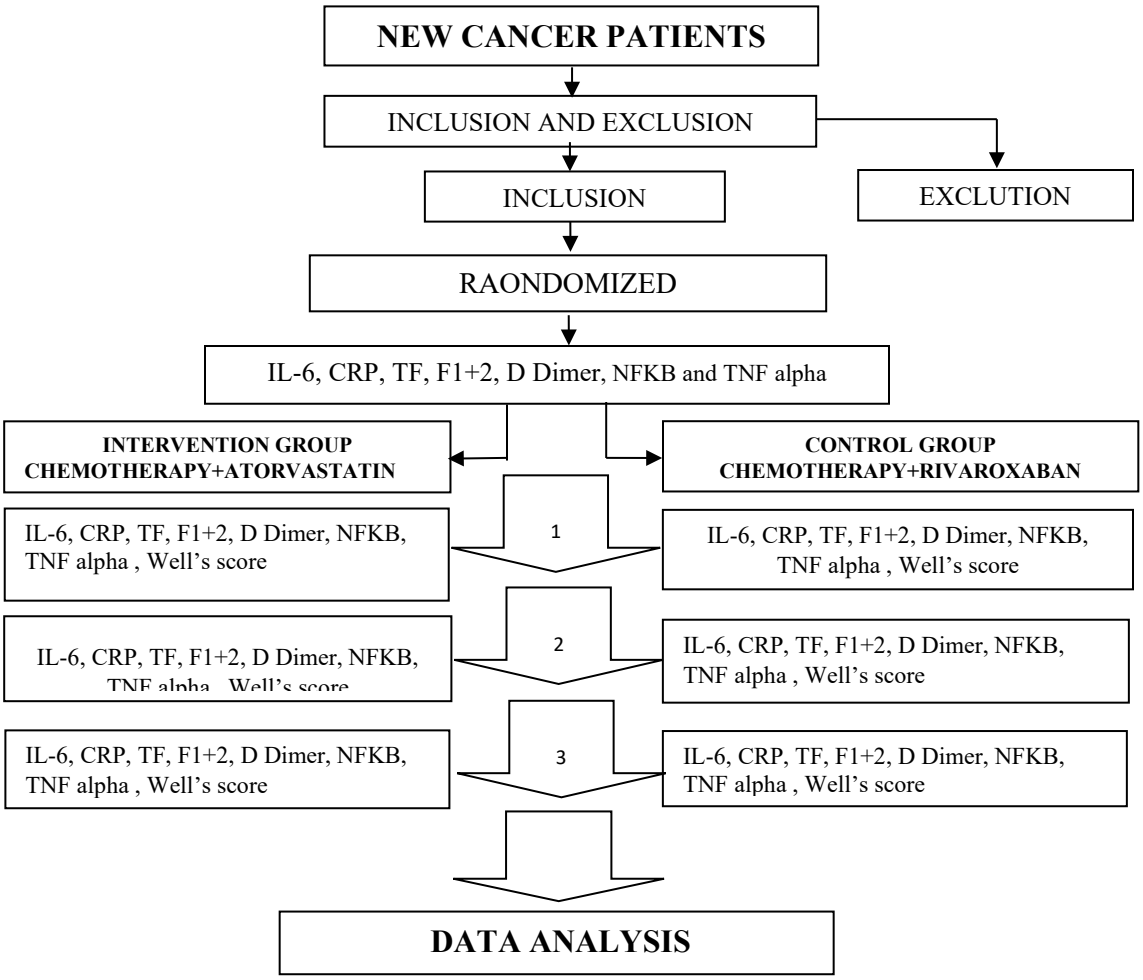


Figure 3. Research Flow

## P. Assessment of the effectiveness and safety of Atorvastatin and Rivaroxaban

### 1. *Primary efficacy end point*

The primary efficacy end point was a decrease in the incidence of proximal or asymptomatic DVT of the limbs diagnosed objectively by Doppler ultrasound of the lower limbs, symptomatic DVT of the upper extremities or distal DVT of the lower limbs, symptomatic or incidental pulmonary embolism, and death from VTE.

**2. *Secondary efficacy end point***

The secondary efficacy end point was a reduction in the incidence of symptomatic VTE and clinically relevant conditions that were not included in the primary efficacy end point, such as death from any cause, arterial thromboembolism found, and visceral thromboembolism found.

**3. *Primary safety end point***

The primary safety end point is the occurrence of major bleeding that meets the criteria of the International Society on Thrombosis and Hemostasis (ISTH). Major bleeding is defined as bleeding that is clinically evident in association with:

1) Decreased hemoglobin of 2 g/dL or more, or
2) Transfusion of 2 or more units of red blood cells, or
3) Bleeding in critical locations such as intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
4) A fatal condition

***4. Secondary safety end points***

Secondary safety end points were the percentage of patients with clinically relevant non-major bleeding such as ISTH criteria, minor bleeding, and bleeding during the intervention period.

Clinically relevant non-major bleeding was defined as significant bleeding that did not meet the criteria for major bleeding but was associated with:

1) Medical intervention
2) Unscheduled contact (visit or phone call) with doctor

3) Temporary discontinuation of the research drug, or

4) Discomfort such as pain, or interference with activities of daily living

**Q. Data Analysis**

Analysis of the effect of atorvastatin compared with rivaroxaban as prophylaxis of deep vein thrombosis in cancer patients at high risk of thrombosis undergoing chemotherapy was performed by Intention to Treat Analysis (ITT).

Data analysis and interpreted to test the proposed hypothesis using statistical software with the following stages:

a. Descriptive Analysis (Univariate)

The data collected was processed and analyzed descriptively. Descriptive statistical analysis is used to describe or provide an overview of the object under study. In this descriptive analysis, the data for the variables are presented in a table to test the equality of the mean values and the frequency distribution of the variable values in the population.

b. Bivariate Analysis

i. Analysis to see the effect of giving atorvastatin compared to rivaroxaban on the incidence of DVT was carried out by using the Chi-Square Test between the atorvastatin group and the rivaroxaban group.

ii. Analysis to compare the effectiveness of atorvastatin and rivaroxaban on the levels of inflammatory biomarkers and biomarkers of coagulation activation on days 30, 60, and 90, a different mean test was performed (unpaired t-test or Mann Whiney test). To determine the mean difference test to be used, the data normality test was carried out using the Shapiro-Wilk test, because the number of samples was less than 50. If the Shapiro-Wilk test obtained data that were normally distributed (p value > 0.05), then the mean difference test was used. is the Independent T Test and if the distribution is not normal, then the test used is the Mann-Whitney U Test.

iii. The analysis to see the effect of atorvastatin and rivaroxaban on decreasing levels of IL-6, CRP, TF, F1+2, D-dimer, NFKB and TNF alpha on days 30, 60,

and 90 between the atorvastatin group and the rivaroxaban group was carried out:

1) Transformation of data in the form of delta by reducing the level of the initial measurement (basic data) with the results of monthly serial measurements.
2) Delta IL-6, CRP, TF, F1+2, D Dimer, NFKB and TNF alpha were analyzed to find out if the data was normal or not, if the data was not normal, it was transformed, if the data was normal, the analysis used the Independent T Test, if the data was not normal, the analysis used Mann-Whitney U Test.

iv. The analysis to see the tendency of decreasing levels of IL-6, CRP, TF, F1+2, D-dimer, NFKB and TNF alpha in the atorvastatin group and rivaroxaban group used the Friedman test.

v. Analysis to see the trend of decreasing levels of IL-6, CRP, TF, F1+2, D-dimer, NFKB and TNF alpha on days 30, 60, and 90 in the atorvastatin group and rivaroxaban group using the Wilcoxon test.

vi. Analysis to see the changes/delta levels of IL-6, CRP, TF, F1+2, D-dimer NFKB and TNF alpha on days 30, 60, and 90 that occurred in the study subjects in the atorvastatin and rivaroxaban groups, transformed numerical data into categorical data. delta levels of IL-6, CRP, TF, F1+2, D-dimer, NFKB and TNF alpha were fixed/down and up. Data analysis was performed with Chi Square.

vii. To see the correlation between levels of the inflammatory biomarker IL-6, CRP, NFKB and TNF alpha and levels of the coagulation activation biomarker TF, F1+2, D-dimer, Spearman's test was performed.

viii. Analysis to see the type of cancer in the atorvastatin and rivaroxaban groups that could not reduce inflammatory biomarkers and activation of coagulation was carried out by the Kruskal Wallis test.

c. Multivariate Analysis

Analysis to see the correlation between the variables with the incidence of DVT, multivariate analysis was carried out with logistic regression using the Nagelkerke R squares method to find out how many percent of the mechanism for the low incidence of DVT was explained by the mechanism of atorvastatin administration.

d. Cost-effectiveness analysis

A cost-effectiveness analysis of the model was performed by comparing two drugs for thromboprophylaxis: (1) Atorvastatin 20 mg/24 hours, and (2) Rivaroxaban 10 mg/24 hours. The analysis was carried out from a health care system perspective, with the main end point being cost per patient without DVT.