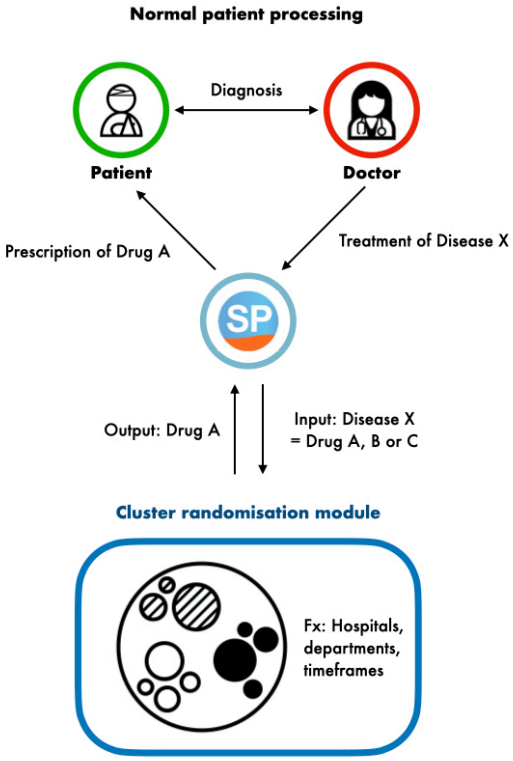
Region Hovedstaden

Cluster-randomized trial of low molecular weight heparins
– Directly through EPIC

EU-CT number: 2022-502402-32-00



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General information

Title: cluster-randomized study of low molecular weight heparins
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Background

Parenteral anticoagulants are used in a variety of settings, including treatment and prevention of venous thromboembolism in cancer patients, medical patients, and surgical patients, along with the use as adjuvant therapy for coronary syndromes.(1-4) The most frequently used parenteral anticoagulants, include the two different low molecular weight heparins; dalteparin and tinzaparin. The two drugs are considered equally efficient and safe regarding treatment and prevention of thrombosis and risk of bleeding.(5) Importantly, there is a lack of evidence regarding whether these drugs are in fact comparable.

The different low molecular weight heparins have different pharmacodynamic and pharmacokinetic profiles. Although, they all act by inhibiting coagulation through inhibition of factor Xa(6) only one study have investigated the drugs head-to-head and this study did not demonstrate any difference in the clinical effect or safety regarding venous thromboembolism, major bleeding, or all-cause mortality. However, a major limitation concerning the study is that it was small and possibly underpowered to detect a clinically important difference. (7)
The aim of this study is therefore to investigate the comparative safety and efficacy of the two different low molecular weight heparins using cluster randomization in patients with an indication for low molecular weight heparins.

Trial purpose

When patients are treated with an anticoagulant, the risk of bleeding increases. It is therefore important to compare the safety profile and the efficacy between the three types of low molecular weight heparins. Identification of treatments with a more favorable safety profile may potentially result in better outcomes and shorter hospital stays. Head-to-head studies of closely related treatments are rare and often difficult to conduct as the effect size is expected to be relatively small and, therefore, the sample size needs to be very large to be able to show a difference. A way of overcoming this challenge is to use cluster randomization i.e. a trial where it is not the patients that are randomized but a unit such as clinical department, a hospital, a geographical region or timeframes such as hours. Applying this method on approved treatments that are already available at the different departments, will make it easier and cheaper to answer the questions regarding the effectiveness and safety of the three low molecular weight heparins. Using this method will allow the inclusion of real-world patients and minimize selection bias. In addition, it can yield benefits for patients, who will potentially receive more effective treatments. Lastly, in a time where the financial burden from rising

healthcare costs is more evident than ever, it has the possibility to save money for hospitals by providing evidence for whether more expensive treatments are actually more effective.

Hypotheses

Based on the literature review, we hypothesize that there is no significant difference in the safety and efficacy when comparing the two low molecular weight heparins; dalteparin and tinzaparin.

Primary main objective

To evaluate whether treatment with any of the low molecular weight heparins will increase the risk of bleeding requiring blood transfusion during admission or death within 30 days in patients with indication for low molecular weight heparins.

Secondary objectives

To investigate the comparable risk in patients treated with dalteparin or tinzaparin regarding:

1. All-cause 30-day mortality
2. All-cause 365-day mortality
3. Blood transfusion during admission
4. Pulmonary embolism at 30 days
5. Heparin induced thrombocytopenia
6. Liver failure
7. Length of hospital admission
8. Days alive out of hospital 30 days

Trial design

Endpoints

Primary main endpoint

Major bleeding requiring blood transfusion and all-cause mortality with in 30 days

Secondary endpoints

1. All-cause 30-day mortality
2. All-cause 365-day mortality
3. Blood transfusion defined from use of SAG-M
4. Pulmonary embolism at 30 days

5. Heparin induced thrombocytopenia (Thrombocytes less than 150 x 10^9/l and presence of HIT antibodies)
6. Liver failure (ALAT 3X upper limit of normal)
7. Length of hospital admission
8. Days alive out of hospital 30 days

Participants

We will include patients admitted to the hospital who has indication for treatment with a low molecular weight heparin. Patients will only be included the first time they are admitted in the period the study run. These patients may include:

1. Patients with deep venous thromboembolism and/or pulmonary embolism
2. Patient that are at an increased risk of developing venous thromboembolism during admission (medical patients)
3. Patients undergoing major surgery, including orthopedic surgery and abdominal surgery
4. Patients with cancer and VTE

Inclusion criteria

- All patients with indication for low molecular weight heparin

Exclusion criteria

- Patients under the age of 18
- Patients who are incapable of understanding the written material received
- Patients who after being informed in writing chooses not to participate
- Patients with contraindications for low molecular weight heparins as described in the SmPC

Pregnancy

Low molecular weight heparins are first-line choice for treatment and prevention of venous thromboembolism in pregnant women and post-partum. It has been shown that dalteparin and tinzaparin does not pass the placenta and animal studies have shown no teratogenic-or fetal toxic properties.(8-10) It has been shown that the heparins are not excreted into the breastmilk.(8-10) The three low molecular weight heparins are used interchangeably, and treatment choice is either based on price or doctor-preference. The potential risk of side effects, will be the same regardless of whether the patient is a vulnerable patient type and the participants will be included in the same way as all the other patients. Thus, the information given to pregnant or breast feeding women will be the same as for all other patients.

Patient discontinuation

A criteria for discontinuation is the patients´ withdrawal of consent from the study and/or withdrawal of consent for us using their data. If the patients withdraws, they will not enter the study and their data will not be used or analyzed. Data regarding withdrawal will be collected via Sundhedsplatformen. The patients will be able to withdraw their consent at any time, and will also receive an email via e-boks 1 month after discharge, describing their participation in the study and the possibility of withdrawing their consent for us using their data.

Study design

A prospective, multicenter cluster randomized study will be conducted, where hospitals in Region Hovedstaden and Region Sjælland will be included, which in total includes 11 hospitals under 9 hospital managements (Herlev and Gentofte Hospital, Rigshospitalet and Glostrup, Bispebjerg and Frederiksberg Hospital, Amager-Hvidovre Hospital, Nordsjællands Hospital, , Næstved-Slagelse-Ringsted Hospital, and Nykøbing Falster Hospital). The randomization will run over a period of 12 months, but may be extended if sufficient endpoints have not been obtained, and the trial will run until the last patient has been followed-up for 12 months.

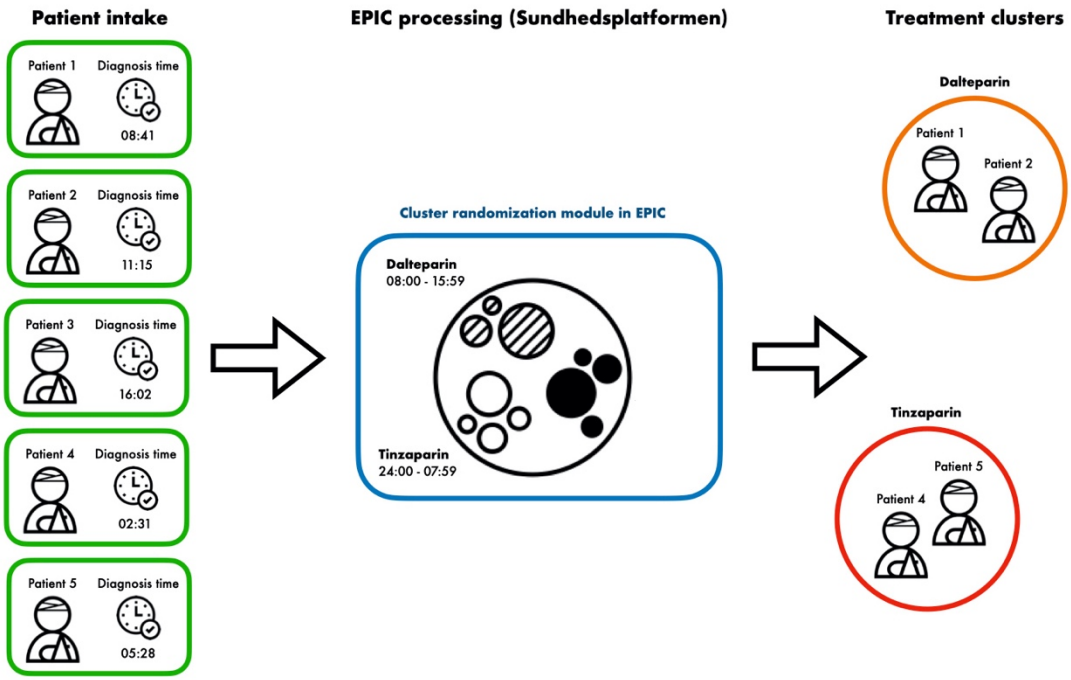

Figure 1: Illustration of study setup

Randomization

A generic module in Epic (Sundhedsplatformen) has been developed that will allow randomization at cluster levels directly from the system. The clusters in this study are time frames of 1 hour, meaning that every hour the recommended choice of pharmaceutical product will change (Figure 1). As an example, from 10-10.59 it will be tinzaparin that is recommended and from 11-11.59 it will be dalteparin that is recommended. Every day the order of the time frames will change, so that it will not be the same time frames where the pharmaceutical products are recommended every day. Since all hospitals in Region Hovedstaden uses Sundhedsplatformen it will be possible to implement the module at all hospitals and all hospital departments that will then run automatically at each hospital. The module will be activated when the medical doctor has decided that the patient has indication for treatment with a low molecular weight heparin and writes either of the two low molecular weight heparins in to the best./ord. in Sundhedsplatformen. The module will be able to report outcomes for all groups of indications. Data extraction on the different specified outcomes will be available through Epic.

Pilottest

A pilot test will be performed at 2 departments at Rigshospitalet (thoraic surgery department and department of cardiology) and 4 departments at Herlev and Gentofte hospital (emergency department, gastroenheden, department of cardiology and department of nephrology). The pilot test will run for 14 days, and will then be evaluated for any errors or problems and the randomization module and study set-up will be updated accordingly.

Blinding

Since this is a cluster-randomized study, the identity of the treatments will not be blinded for the patients or caretakers.

Treatment

Since there are different indications for the use of low molecular weight heparins, dosages will depend on the indication for treatment. Table 2 show the different dosages for the two low molecular weight heparins being investigated according to indication.

Table 1: dosages according to the specific low molecular weight heparin and according to dosage

Indication dosages	**Dalteparin**	**Tinzaparin**
Thromboprophylaxis moderate risk (Abdominal surgery)	• 2.500 IE s.c. 1-2 hours before operation. • Followed by 2.500 IE s.c. s.d. for 5 days dependent on the patient´s mobilization	• 3.500 anti-X_a IE s.c. 2 hours before operation. • Followed by 3.500 anti-X_a IE s.d. until discharge

Tromboprophylaxis high risk (orthopaedic surgery)	• 5.000 IE s.c . the evening before the operation
	  ○ Followed by 5.000 IE s.c. s.d.. for 5 days dependent on the patient´s mobilization
	• Alternatively on the day of operation 2.500 IE s.c. 1-2 hours before operation and 2.500 IE s.c. 12 hours later.
	  ○ Followed by 5.000 IE s.c. s.d..for days dependent on the patient´s mobilization
		• 4.500 anti-X_a IE s.c. 12 hours before operation.
		• Followed by 4.500 anti-X_a IE s.c. s.d. for 7-10 days dependent on the patient´s mobilization

Tromboprophylaxis Medical patients	• 5.000 IE sc s.d.	• Moderat risk: 3.500 anti-Xa IE s.c. s.d.. • High risk: 4.500 anti-Xa IE s.c. s.d.
Treatment of DVT or PE	• 200 IE/kg s.c. daily distrubuted on 1-2 doses, maximum 18.000 IE a day.	Injection fluid 20.000 anti-X_a IE/ml. • 175 anti-X_a IE/kg s.c. s.d.
Treatment in cancer	1st month treatment • 200 IE/kg s.c. s.d., max 18.000 IE daily 1. – 6. months treatment, often extended for a longer time period • 150 IE/kg s.c. s.d.	• 175 anti-Xa/kg s.c. s.d. for 3-6 months
Pregnancy	• 5000 IE s.c. s.d.	• 4500 IE s.c. s.d.

s.d. : once daily, b.i.d. : twice daily, s.c.: subcutaneaous

Statistics

Categorical variables will be presented as counts with percentages(11) Continuous variables will be presented as mean and standard deviations in case of normal distributed data, and as medians and interquartile range in case of non-normal distributed data. (12) Patients will be followed from randomization for up to 30 days and 12 months and the study end when the last patient has been followed up for 12 months. Absolute risk of the primary and secondary outcomes will be estimated by crude cumulative incidence curves, taking into account death as a competing risk. (13) The relative risks of the primary and secondary outcomes will be based in intention to treat analyses, using the Cox proportional-hazards model. As per standard in cluster randomized studies we will include an additive factor for site (hospital) and for seasonality (in practice a factor variable for each two week window). A violation of the assumptions of proportional hazards will be examined and the model will be tested for significant interactions. A p-value of 0.05 will be considered statistically significant, i.e the significance level is α=0.05. Data management and statistical analysis will be performed using SAS (Statistical Analytical System, version 9.4, SAS Institute, Gary, NC.) and R Core Team (2017).(14) In case of changes in the statistical analysis plan, these will be made and logged on clinicaltrials. com

Sample size and power

Approximately 650.000 patients are admitted to a Hospital in Region Hovedstaden each year. Approximately 10% of the patients receive a low molecular weight heparin during their hospital stay, which will result in the randomization of 65.000 patients, distributed on two groups of 32500 patients (dalteparin, tinzaparin). Assuming a 5% risk in one of the groups we have 90% power to detect a difference of 0.5% (so for instance 5% in one group and 5.5 in the other).

Subgroups

Subgroup analyses will be performed according to the following subgroups:

1. Patients who received a low molecular weight heparin as thromboprophylaxis
2. Patients who received a low molecular weight heparin as treatment for thrombosis
3. Patients with cancer
4. Medical patients
5. Patients undergoing surgery (including abdominal and orthopaedic)
6. Pregnant women, antepartum and post-partum
7. Patients under 64 and above 65 years of age
8. Patients with nephropathy
9. Men versus women

The module in epic will be able to report the number endpoints in the specified subgroups and in subgroups with more than 2000 patient.

Outcome assessment

Justification of endpoints

Primary endpoints

The study is designed to assess both the possible beneficial effects and possible side effects of the two low molecular weight heparins. When treated with any of the low molecular weight heparins, there is an increased risk of bleeding regardless of therapeutic agent. It is known that anticoagulation therapy, regardless of type and administration route is associated with increased hospital mortality.(15) This emphasizes the need to investigate the risk-benefit profile of the two different low molecular weight heparins with respect to bleeding and all-cause mortality.

Secondary endpoints

The secondary outcomes have been chosen because these are clinically relevant complications to treatment with low molecular weight heparins. Heparin induced thrombocytopenia is a condition where the immune system is triggered to cause a low platelet count. Despite of a low platelet count, patients are at a high risk of experiencing clotting.(16)

Safety

Adverse events

An adverse event is defined as any untoward medical occurrence, including an exacerbation of a preexisting condition, in a patient that has received a pharmaceutical product. The relationship between the treatment and adverse event does not have to be causal.

A serious adverse event is any adverse event that has resulted in the death of a patient, that is immediately life threatening, that results in persistent or significant disability or incapacity of the patient, is a congenital anomaly /birth defect or is to be deemed serious for any other reason. If it is an important medical event when based upon appropriate medical judgement which may jeopardize the patient and may require medical or surgical intervention.

Adverse events of special interest: Since the study purpose is to investigate the risk of adverse events, please refer to the section where the endpoints are defined. All possible adverse events are listed in table 3. In addition an adverse event that leads to hospitalisation or prolongation of hospitalisation is considered serious.

Risks, side effects and other disadvantages

The risk of adverse events in the study is deemed moderate. Dalteparin and tinzaparin have been approved by the Danish Medical Agency for the treatment and prevention of venous thromboembolism in Denmark. The side effects that can be experienced varies according to which low molecular weight heparin that is used (table 3)

Table 2: Possible side effects according to pharmaceutical product and according to frequency.

Frequency of side effects	**Dalteparin**	**Tinzaparin**
Very frequent (more than 10 out 100)	Bleeding tendency Thrombocytopenia (type 1) Increase liver transaminases Alopeci	Bleeding tendency Anemia haematoma
Frequent (10 out 100)	Thrombocytopenia (type II) Allergic reactions Cerebral hemorrhage	Thrombocytopenia (type 1) Allergic reactions Bullous dermatitis

Not frequent (1 out 100)	Hyperkaliemia Skin nekrosis	Thrombocytopenia (type II) Allergic reactions, including anaphylaxis Hyperkaliemia Osteoporosis Priapism Skin necrosis
Rare (1 out 1000)	Spinal haematoma Bleeding (retroperitoneal)	

Reporting of adverse events

Article 41, part 2 of the CTR provides the possibility for protocol-specified adaptions to the procedures for recording and reporting of adverse events, when the study is considered a low-interventional trial. This means that for a low interventional trial it is not necessary to report all adverse events as in a traditional randomized trial. Since the intervention in this study is also the standard treatment, it is not expected to find any unpredicted adverse events other than those already stated. The yearly safety report, will assess the risk of the primary endpoint, all-cause mortality or blood transfusion requiring bleeding. The safety committee can ask to see other end points, which can be extracted from Sundhedsplatformen.

Quality control and data monitoring

The clinical trial will be conducted in compliance with the protocol, with the Regulation (EU) No 536/2014 and with the principles of good clinical practice. An independent safety monitoring committee (SMC) will be assembled and will consist of two cardiologists. They will monitor data regarding the safety of the low molecular weight heparins. Interim analyses will be performed every month to closely monitor the intervention, where a data extract of the primary endpoint will be sent to the safety committee that will asses this, and end the study in case of any safety issues, E.g. if there are any major differences between the low molecular weight heparins, that will make it unethical to continue the study. This could for instance be, if one of the pharmaceutical products shows a very high a number of major bleeding events. The SMC will maintain all monitoring duties as outlined in CTR Art 48, with regards to the rights of the subjects, and the reliability and robustness of data collected. The sponsors confirms that the investigators and SMC involved in the clinical trial can perform clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents, this includes the inspection of withdrawal of consent. Each year the sponsor will submit an annual safety report in in accordance with Art 43. A single annual safety report will be submitted covering the two investigational medicinal products.

Ethics

Ethical comittee

The study will be approved by the medical ethical committee in Denmark (MVK). According to EU-legislation, informed consent can, in cluster randomized trials, be obtained by simplified means. No serious adverse events are expected other than the ones already stated.

Ethical justification of the trial

With an increasing number of especially elderly patients, more patients will receive one of the low molecular weight heparins in the future. The three pharmaceutical products are already approved in Denmark and has been used for many years. The side effects are already known, and the risk benefit regarding the prevention and treatment has been outweighed by the inherent risk of bleeding. In this study, patients will only receive a low molecular weight heparin according to national and international guidelines in which they are considered equipoise, thus participation in the study is considered very low risk. Data from this study will provide the opportunity to investigate if the two pharmaceutical products are in fact equally effective and safe and will answer the question whether it is legitimate to focus primarily on cost. Overall, it has been assessed that the advantages of conducting this study outweigh any disadvantages through a favorable ethical balance, since the choice of pharmaceutical product will be replaced with a systematic choice rather than a subjectively or arbitrarily choice.

Informed consent process

As of January 2022, the new clinical trials regulation was implemented. With the new regulation (EU regulation No 536/2014 of the European parliaments and of the council of 16th of April 2014 on clinical trials on pharmaceutical products for human use article 30 (informed consent in cluster trials)), it has been decided that the traditional informed consent can be omitted in cluster-randomized trials. This means that informed consent can be obtained by simplified means, meaning that the informed consent can be given based on written material, and if the participants does not object, this is considered as a consent. However, this can only be done if the participants are given information in accordance with what is described in the protocol, and that the information material makes it clear that the participants can refuse to participate in the study or withdraw at any point without any resulting detriment – and that after the participant has been informed, the patient does not object to participating in the trial. Additional conditions must be fulfilled:

a) The simplified means does not contradict national law

b) The methodology requires groups of participants rather than individual subjects (justified in section; purpose of trial)
c) The clinical trial is low-intervention and that the pharmaceutical products are used in accordance with the terms of the marketing authorization (The two low molecular weight heparins are only investigated in patients with the indications specified in the marketing authorization, in addition these are drugs that are already used in the everyday clinical practice, where the choice as of now is mainly based on pricing)
d) There are no interventions other than the standard treatment of the subjects concerned.
e) The protocol justifies the reasons for obtaining informed consent with simplified mean and describes the information given to the patients.

Information material to patients

All patients will be given written information material when they are admitted to the hospital and have indication for a low molecular weight heparin. The information will be written in lay man terms and in different languages, and will comply with what is described in the protocol and will state that the patients can refuse to participate and can withdraw at any time. In addition, it will be pointed out that opting out will not have any influence on the patient's further treatment. After patients have been discharged, they will also receive an email through E-boks describing that they have been included in the study and that they can choose not to participate in the study by actively withdrawing their consent.

Information to healthcare professionals and hospital departments

All healthcare professionals will be informed both verbally and with written material, explaining both the study design and how the module works in Sundhedsplatformen.

Activities

The trial will run at all hospitals and all departments in Region Hovedstaden. The management at each hospital has been contacted and have signed a site suitability form, stating that they have the facilities and equipment (Sundhedsplatformen) and have suitable agreements in place to ensure that the trial can run. At each site a contact person has been appointed, whom have agreed to comply with the protocol of DANHEP, and are informed about the informed consent process by simplified means and are instructed on how to handle the process of informed consent by simplified means.

Meetings

Meetings have been arranged with all hospital directors in December 2022 and January 2023, where the sponsor (Lars Køber), principal investigator (Kasper Iversen) and investigator (Caroline Sindet) have given or will be giving a presentation of the project.

Before the presentations, hospital directors have been asked to appoint a contact person from their hospital, who will also act as the main contact person for that hospital (Site). This contact person will also join the steering committee, in which we will seek to have the steering committee represent the departments that most often use low molecular weight heparins, namely: cardiology, surgical, gynecological and obstetrics, internal medicine and nephrology departments.

Roles and responsibilities

The roles and responsibilities of the hospital management, contact person and investigators are as follows:

- Hospital management: responsible for appointing contact persons and follow up with these.
- Contact persons: responsible for informing relevant departments about the study, organize information meetings, be the link to the primary investigator and participate in steering committee meetings.
- The investigators: responsible for all information material, including written information for patients and written and visualization material for staff), answer questions from contact persons.

Organization of training at departments

Daily trialist (Caroline Sindet) will be in charge of daily operations, but will have the possibility to delegate certain tasks to the members of steering committee and other investigators. These tasks include:

1. The preparation and distribution information material to local health professionals which includes:
    a. **Medical doctors** who prescribe low molecular weight heparins (Video and written material about the project, pocket cards regarding dosages)
    b. **Nurses** who administers low molecular weight heparins (Video and written material about the project, and pocket cards regarding dosages)

   c. **Secretaries** (Information material on distribution of information material to patients, and Information material describing how to exclude patients from the study in sundhedsplatformen)
2. The organization of training at local deparrtments which includes physical meetings, presentations and webinars about the study, and training of nurses in administering all three low molecular weight heparins. A limited amount of training of employees is necessary, as the pharmaceutical products are well known and are already being used in the different departments. However, it is important to ensure that the nurses are comfortable giving both pharmaceutical products, as they can be given in different dosages and in different intervals. Hence it is important to ensure that they are familiar with the various pharmaceutical products.
3. The organization and monitoring of changes in Sundhedsplatformen.

Costs

The patients will have no extra costs in relation to the trial, as low molecular weight heparins are handed out free of charge at the hospitals. This is because the negotiated price of the low molecular weight heparins is lower when received from the hospital pharmacies compared with the prices at the community pharmacies and thus the Region has an incentive for the patients to collect the free-of charge low molecular weight heparins at the hospital pharmacies. The hospitals will also not have any additional costs, since the most frequently used low molecular weight heparin, tinzaparin, is also the most expensive agent costing 11 DKK/DDD compared with dalteparin costing 7.3 DKK/DDD.

Confidentiality

Investigators, sponsor, Danish Medicines Agency are subject to confidentiality. All collected data will be handled according to the personal data law, and GDPR.

Declarations of interests

None

Data management and extraction

Data will be entered electronically in EPIC (sundhedsplatformen) hosted by Region Hovedstaden. The Data Protection Regulation and the Data Protection Act are complied with. A list of variables is provided in appendix I. Sponsor and investigator are responsible for ensuring that the data protection rules are complied with in relation with the processing of personal data.

Publication and sharing of data

The investigators will be co-authors on all publications. Caroline Sindet-Pedersen will be first author and Kasper Iversen and LK will decide the rest of the author list on the planned main paper, and on the following sub-studies. In addition, members of the steering committee will also have the opportunity of contributing to one or more manuscripts. Both positive and negative results will be published in international peer-reviewed journals. If this is not possible, the results will be made public through a website. In addition results will be published in CTIS as soon as possible and no later than 1 year after the trial ends.

Timeline

The study is expected to start 1st of April 2023 both Region Hovedstaden and Region Sjælland. The study will run for 12 months or longer if necessary. All patients will be followed up for 1 year after they have been included.

Financing

The project has been budgeted to 4 million Dk.

Remuneration

No remuneration is provided to the study participants

Patient insurance

Insurance of patients is secured via Patienterstatningen

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Appendix I: Variable list

Variable	Outcome	Comment/descritpion of variables
Patient information		
CPR number	Number	Personal identification code
Date of birth	Year-month-day	
Sex	1=woman, 2=man	Biological sex
Weight	Number	Lastest registered weight of patient
Death status		
Time of death	Year-month-day	
Pat_status_navn	1=alive, 2=dead	If the patient is dead or alive
SP variables		
PAT_ENC_CSN_ID	Number	Unique ID for treatment contact
Kvalitetsarbejde_j_n	J=Yes, N=No	If the patient is willing to participate in quality work
forskning_j_n	J=Yes, N=No	If the patient is willing to participate in research
Localisation of admission		
Adt_department	Number	Department number
Hospital_id	Number	SKS code
Adt_department_Id	Number	Department code
Afsnit_navn	Name	Department name ex. BFH AKUTMODTAGELSE BH
Afsnit_speciale	Name	Medical speciality
ICD-10 codes	Number	Primary ICD-10 code related to admission
Operation codes	Defined from surgical procedure codes NSCP	Primary surgical codes related to admission
Admission and discharge		
Hosp_admsn_time	Year-month-day	Admission time
Hosp_disch_time	Year-month-day	Time of discharge
Hosp_adt_pat_class_c		Latest available patient class

Medication (only for Low molecular weight heparin)		
Tinzaparin Dalteparin	Name	Name of low molecular weight heparin
Strength	Unit	Unit Can both be mg/ml and anti-X_a IE
Administration route		Subcutan/IV
ATC-code	Defined from ATC codes	B01AB10= Tinzaparin B01AB04= Dalteparin
Dosage	Number	
Administration time	Year-month-day	Time when the low molecular weight heparin is given
Ordination time	Year-month-day	Time when the ordination of the low molecular weight heparin was placed. Variable created in SP with the randomization module
Indication	1. Postoperative thromboprophylaxis 2. immobilization 3. Treatment deep venous thromboembosis 4. Treatment pulmonary embolism 5. NSTEMI, 6. Bridging,	Indication for administering a low molecular weigh heparin. Variable created in SP with the randomization module.
Randomised	Yes/No	Whether the patient was randomized
Variables in relation to admission		
Blood samples (up to 6 months prior to inclusion and during admission)		
eGFR	Value + date of blood sample	NPU code: DNK35302, DNK35301
Creatinine	Value + date of blood sample	NPU: NPU04998, NPU18016, NPU17559
ALAT	Value + date of blood sample	NPU code: NPU19651
Hæmoglobin	Value + date of blood sample	NPU code: NPU02319
Erythrocytter	Value + date of blood sample	NPU code: NPU01960
Trombocytter	Value + date of blood sample	NPU code: NPU03568
Albumin	Value + date of blood sample	NPU Code : NPU19673, NPU01132
Pregnancy		
Edema, proteinuria and hypertension during pregnancy, labour and postpartum	Defined from ICD-10 codes	ICD-10: DO10-DO16
Venous complications	Defined from ICD-10 codes	ICD-10: DO22

during pregnancy		
Birth complications	Defined from ICD-10 codes	ICD-10: DO60-DO75
Birth	Defined from ICD-10 codes	ICD-10: DO80-DO84
Venous complications postpartum	Defined from ICD-10 codes	ICD-10: D087, D088
Outcomes (registered up to 1 year after inclusion)		
eGFR	Value + date of blood sample	NPU code: DNK35302, DNK35301
Creatinine	Value + date of blood sample	NPU: NPU04998, NPU18016, NPU17559
ALAT	Value + date of blood sample	NPU code: NPU code: NPU19651
heparin-PF4-Ab/IgG)HIT;P	Value + date of blood sample	NPU code: NPU27799
Hæmoglobin	Value + date of blood sample	NPU code: NPU02319
Erythrocytter	Value + date of blood sample	NPU code: NPU01960
Thrombocytes	Value + date of blood sample	NPU code: NPU03568
Albumin	Value + date of blood sample	NPU code: NPU19673, NPU01132
Bloodtransfusion	Value + date of blood sample	SAG-M, thrombocytter, plasma
Admission time	Number	Discharge date – admission date
Deep venous thrombosis	Defined from ICD-10 codes	ICD-10: DI80, DI821, DI822, DI823, DI828, DI829, DO87
Pulmonary embolism	Defined from ICD-10 codes	ICD-10: DI26
Shift to oral anticoagulant	Defined from ATC-codes	ATC: B01AA03, B01AA04, B01AF01, B01AF02, B01AE07
Death	Year-month-day	Time of death and cause of death
Baseline variables (ICD-codes registered up to 10 years prior to inclusion)		
Deep venous thrombosis	Defined from ICD-10 codes	ICD-10: DI80,DI821,DI822,DI823,DI828, DI829
Pulmonary embolism	Defined from ICD-10 codes	ICD-10: DI26
Ischemic heart disease	Defined from ICD-10 codes	ICD-10: DI20-25
Peripheral artery disease	Defined from ICD-10 codes	ICD-10: DI70
Acute myocardial infarction	Defined from ICD-10 codes	ICD-10: DI21, DI22
Stroke	Defined from ICD-10 codes	ICD-10: DI63, DI64

Atrial fibrillation	Defined from ICD-10 codes	ICD-10: DI48
Cancer	Defined from ICD-10 codes	ICD-10: DC
Chronic kidney disease	Defined from ICD-10 codes	ICD-10: DE102, DE112, DE132, DE142, DI120, DN02, DN03, DNO4, DN05, DN06, DN07, DN08, DN11, DN12, DN14, DN158, DN159, DN160, DN162 , DNI63, DN164, DN168, DN18, DN19, DN26, DQ61, DM300, DM313, DM319, DM321B
Hypertension	Defined from diagnoses codes or treatment with 2 or more antihypertensive drugs: adrenergic α-antagonists, non-loop diuretics, vasodilators, β-blockers, calcium channel blockers, renin-angiotensin system inhibitors.	ICD10: I10-15 ATC: C02A, C02B, C02C, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C02DA, C09BA, C09DA, C02DB, C02DD, C02DG, C07A, C07B, C07C, C07D, C07F, C08, C09BB, C09DB, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52, C03C, C03EB
Liver disease	Defined from ICD-10 codes	ICD-10: DB15, DB16, DB17, DB18, DB19, DC22, DD684C, DK70, DK71, DK72, DK73, DK74, DK75, DK76, DK77, DZ944, DQ618A
Chronic obstructive pulmunary disease	Defined from ICD-10 codes	ICD-10: DJ42, DJ43, DJ44
Heart failure	Defined from ICD-10 codes	ICD-10: DI110, DI42, DI50, DJ81
Coagulopathy	Defined from ICD-10 codes	ICD-10: DD685, DD686
Diabetes mellitus	Defined from glucose-lowering medication and ICD-codes	ATC: A10 ICD-10: DE10, DE11
Previous surgery	Defined from procedure codes	NSCP: KA-KT
Pharmacotherapy (registered 1 year prior to inclusion and up to 30 days after inclusion)		
Adenosine-phosphate receptor antagonists	Defined from ATC codes	ATC: B01AC04, B01AC22, B01AC24
Aspirin	Defined from ATC codes	ATC: B01AC06 N02BA01
Non-steroidal-anti-inflammatory-drugs	Defined from ATC codes	ATC: M01A, except M01AX05
Beta-blockers	Defined from ATC codes	ATC: C07A, C07B, C07C, C07D, C07F
Calcium channel blockers	Defined from ATC codes	ATC: C07F, C08, C09BB, C09DB
Renin-angiotensin system inhibitors	Defined from ATC codes	ATC: C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Diuretics	Defined from ATC-codes	ATC: C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C02DA, C09BA, C09DA, C09xa52
Oral contraceptives	Defined from ATC-codes	ATC: G03A
Hormone replacement therapy	Defined from ATC-codes	ATC: G03C, G03D, G03E, GO3F

Ulcus medication	Defined from ATC-codes	ATC: A02
Lipid modifying drugs	Defined from ATC-codes	ATC: C10
Oral anticoagulation therapy	Defined from ATC-codes	ATC: B01AA03, B01AA04, B01AF01, B01AF02, B01AE07