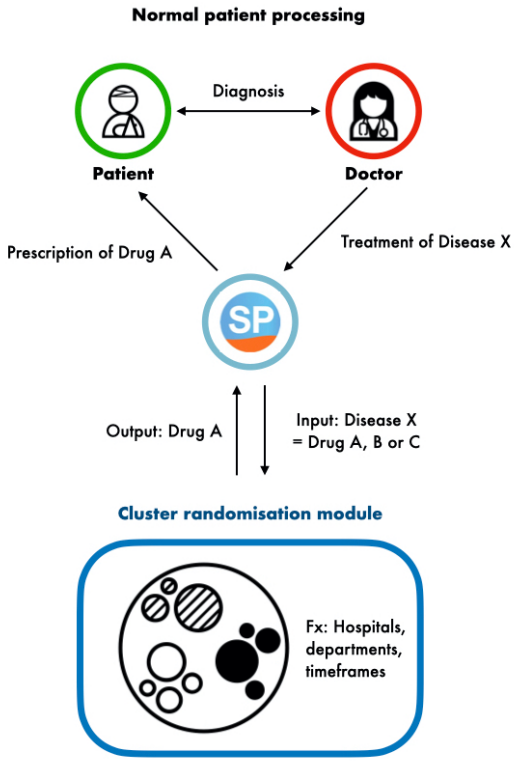
Region Hovedstaden

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

EU-CT number: 2022-003380-15



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 (dalteparin and tinzaparin) using cluster randomization in patients with an indication for low molecular weight heparins.

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

Study design

A prospective, multicenter cluster randomized study will be conducted, where all hospitals in the two regions; Region Hovedstaden and Region Sjælland will be included, which in total includes 10 hospitals (Herlev and Gentofte Hospital, Rigshospitalet, Bispebjerg Hospital, Amager-Hvidovre Hospital, Glostrup Hospital, Nordsjællands Hospital, Holbæk Hospital, Slagelse Hospital, Køge and Roskilde Hospital, Nykøbing Falster Hospital). The trial will run over a period of 12 months, but may be extended if sufficient endpoints have not been obtained.

Development of module in epic and randomization

A generic module in Epic 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. Within the specified timeframe, each patient will be randomized to one of the 2 treatments (dalteparin, or tinzaparin) (Figure 1). 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.

Statistics

Categorical variables will be presented as counts with percentages(8) 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. (9) Patients will be followed for up to 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. (10) The relative risks of the primary and secondary outcomes will be based on intention to treat analyses, using the Cox proportional-hazards model. 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 $\alpha=0.05$. 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).(11)

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).

Ethics

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 three 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 three 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.

Sponsor

Lars Køber, MD, DMsc, Professor
Department of Cardiology, Rigshospitalet,
Blegdamsvej 9, 2100 københavn
lars.Koeber.01@regionh.dk
Phone:

Principal investigator

Kasper Karmark Iversen, MD, DMSc, Clinical Professor
Department of Emergency Medicine and department of cardiology, Herlev and Gentofte Hospital
Borgmester Ib Juuls Vej 1, 2730 Herlev
kasper.karmark.iversen@regionh.dk
Phone: +4538686009

References

1. Merli GJ, Groce JB. Pharmacological and clinical differences between low-molecular-weight heparins: implications for prescribing practice and therapeutic interchange. P & T : a peer-reviewed journal for formulary management 2010;35:95-105.
2. NBV, Dansk Cardiologisk Selskab, www.cardio.dk, Lungeemboli
.
3. NBV, Dansk Cardiologisk Selskab, www.cardio.dk, Akut koronart syndrom.
4. Vardi M, Zittan E, Bitterman H. Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism. The Cochrane database of systematic reviews 2009:Cd006771.
5. Yang H-q, Liu M-c, Yin W-j, Zhou L-y, Zuo X-c. Safety and Efficacy of Low Molecular Weight Heparin for Thromboprophylaxis in the Elderly: A Network Meta-Analysis of Randomized Clinical Trials. Front Pharmacol 2021;12.
6. Collignon F, Frydman A, Caplain H et al. Comparison of the pharmacokinetic profiles of three low molecular mass heparins--dalteparin, enoxaparin and nadroparin--administered subcutaneously in healthy volunteers (doses for prevention of thromboembolism). Thrombosis and haemostasis 1995;73:630-40.
7. Wells PS, Anderson DR, Rodger MA et al. A randomized trial comparing 2 low-molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. Archives of internal medicine 2005;165:733-8.
8. Betty R. Kirkwood JACS. Chapter 17. Chi-squared test for 2x2 and larger contingency tables. Medical Statistic 2. ed. Oxford, UK: Blackwell Science Ltd. , 2003:165-176.
9. Altman DG. Principles of statistical analysis. Practical statistics or medical research. 8 ed. London: Chapman & Hall, 1999:152-177.
10. Altman DG. Analysis of survival times. Practical statistics for medical research. London: Chapmann & Hall, 1999:365-394.
11.
. R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.