
# *F*requency of vascular *e*vents using "short treatment"*t*hrombosis prophylaxis after fast-track hip and knee *a*rthroplasty

# FETA-study

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# *F*requency of vascular *e*vents using "short treatment" *t*hrombosis prophylaxis in fast-track hip and knee *a*rthroplasty (FETA-study)

A prospective descriptive cohort study using prophylaxis for 3±2 days in patients receiving fast-track elective hip or knee arthroplasty

In cooperation with the Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement(LCFHK).

**Project leader and coordinating investigator:**

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**Clinical responsibility:**

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**Other investigators:**

Per Kjærsgaard-Andersen MD, Sygehus Lillebælt

Torben Bæk Hansen MD, Professor, Regionshospitalet Holstebro

Henrik Husted, MD, Hvidovre Hospital

Lars-Peter Jorn, MD, Regionshospitalet Viborg

Mogens Berg Laursen, MD, Ortopædkirurgien Nordjylland

Lars Tambour Hansen, MD, Sydvestjysk Hospital Grindsted/Esbjerg

**Statistics:**

Christoffer C. Jørgensen, external statistical assistance can be requested if necessary.

**Study sites:**

Orthopedic departments: Århus University Hospital THG, Hvidovre Hospital, Ortopædkirurgien Nordjylland (Farsø), Regionshospitalet Holstebro, Sygehus Lillebælt, Regionshospitalet Viborg and Sydvestjysk Sygehus Grindsted/Esbjerg.

## Background:

Surgery is recognized as being related to the development of thrombosis, especially after major orthopedic surgery (1;2). These complications are defined as venous thromboembolic events (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE).

Pharmacological prophylaxis reduces the risk of thrombosis and recommendations (grade 1a)from the American College of Chest Physicians (ACCP) are one of three following anticoagulantia:

1: Low molecular weight heparin (LMWH)
2: Faktor Xa-inhibitors
3: Vitamin-K-antagonists
Recommended duration of thrombosis prophylaxis is 10 days after total knee arthroplasty (TKA) and 35 days after total hip arthroplasty (THA) (3).

In the United States of America most surgeons follow ACCP guidelines. Studies have shown that about 90 % of surgeons adhere to guidelines, however, many use additional prophylaxis such as compressive stockings(4). More recent investigations find a lower compliance amongst surgeons world wide of about 50% (5). There are disagreements about the validity of the before mentioned guidelines due tothe many exclusion and inclusion criteria in the analyzed studies and due to the fact that it is the thoracic surgeons who dictate the orthopedic surgeons guidelines(6), therefore the American Academy of Orthopedic Surgeons (AAOS has developed their own guidelines. The main difference between ACCP and AAOS guidelines is the use of compressive stocking and acetylsalicylic acid as only prophylaxis in patients at risk of bleeding and a general disagreement on the relationship of DVT and PE(7).
In Denmark, the Danish Society of Orthopedic Surgeons (DSOS) has their own guidelines of 7 days of postoperative thrombosis prophylaxis which illustrates the controversies in this area.

The few studies who do not comply with ACCP guidelines, using acetylsalicylic acid (and early mobilization) as only prophylaxis show very low frequencies of vascular events (8-11), raising doubts about the best choice of treatment, especially considering increased mortality with LMWH compared to acetylsalicylic acid(12).

Preliminary uncontrolled studies in TKA have shown that early mobilization (<24 hours after surgery) reduces risk of postoperative VTE in patients treated with LMWH(13), and as frequency of DVT following TKA is decreasing over time using warfarin (VKA) as prophylaxis(14), interest in postoperative mobilization is increasing.

The trend towards enhanced recovery protocols (fast-track surgery) where optimized pain treatment, early mobilization (<24 hours), preoperative patient information etc. aims to decrease length of hospital stay. Data on THA and TKA patients from Hvidovre Hospital proves that 92 % of patients were discharged within 5 days and 41 % within 3days(15).

An un-published preliminary study from Hvidovre Hospital in about 2000 patients shows very low frequency of symptomatic VTE in 90-days follow-up, with mortality of 0.15%, DVT/PE/death in TKA of 0.66%

and 0.52% in THA when using a fast-track setup (16). This is lower than comparable literature with thrombosis prophylaxis for 35 days postoperatively.

A group of experts has suggested that pharmacological thrombosis prophylaxis in patients with early mobilization is non-obligatory, this would result in decreased side-effects such as bleedings, less inconvenience in the patients and economical advantages(17). This has resulted in short prophylaxis treatment being standard of care in several departments in Denmark (i.e. Hørsholm, Hvidovre and Farsø hospitals).

No previous study has been published with a detailed description on the risk of vascular events, including arterial complications, using short-treatment thrombosis prophylaxis in a fast-track setup after THA/TKA or commented on identification of risk factors(2;18;19).

It must be mentioned that Asian patients (Korea, China etc.) do not have a tradition for thrombosis prophylaxis after THA due to the low frequencies of VTE without prophylaxis. In this context, differences in genetics and dietary habits etc. must be considered (20;21).

# 1. Intention of study

## 1.1 Primary outcome

To conduct a high quality cohort study to investigate the frequency of symptomatic DVT, PE, acute myocardial infarction (AMI, stroke and other vascular events and/or death of other causes in patients having elective uni and bilateral THA/TKA, revision THA/TKA and uni-KA in a fast-track setup including short treatment thrombosis prophylaxis(3 ± 2 days). Additionally, identification of risk factors for such events will be attempted (Appendix 4).

## 1.2 Hypothesis

No increased frequency of symptomatic thromboembolic events in THA/TKA in a fast-track setup with short treatment thrombosis prophylaxis.

# 2. Participants and methods

## 2.1 Design

A detailed prospective multicenter high quality cohort study of about 5000 patients > 18 years old, having elective uni- or bilateral THA/TKA, revision and uni-KA with thrombosis prophylaxis only during hospitalization (3 ± 2 days/ 72 ± 48 hours). Follow-up is 90 days. Patients with postoperative clinical

symptoms of vascular events are encouraged to seek a physician in order to receive relevant examination and treatment (se appendix 3).

## 3. Patient selection

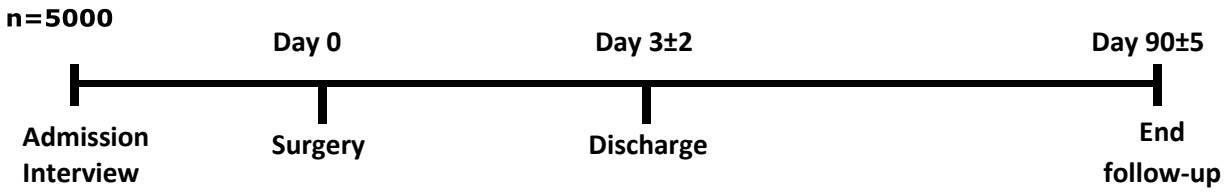
Patients will be included from the Orthopedic departments of: Århus Sygehus, Tage Hansens Gade, Regionshospitalet Holstebro, Hvidovre Hospital, Sydvestjysk sygehus Grindsted, Vejle Hospital and Ortopædkirurgien Nordjylland (Farsø), starting ultimo December ´09 til December ´11, 5000 patients need to be included. In all centers mean length of hospital stay (LOS) is short, with discharge before day 3 ± 2**.** LOS is defined as number of nights spent in hospital after surgery.

### 3.1 Inclusion criteria

- Males and females> 18 years old
- Primary uni/bilateral THA/TKA, revision THA/TKA and uni-KA in fast-track setup
- Discharge on day 3 ± 2/72 ± 48 hours

**Observations and tests**

### 3.2 Plan:




**Day -7 til -1**:

The patient goes through physical examination and demographics are registered (appendix 4).

**Dag 0**: defined as day of surgery

Patient has surgery

Thrombosis prophylaxis according to local guidelines (appendix 1).

**Dag 3** ± **2:** Patient is discharged (4.3) and ceases thrombosis prophylaxis.

**Dag 90** ± 5:End follow-up

### 3.3 Discharge criteria

- Independent in daily activities
- In/out of bed
- In/out of chair
- Independent walk with mobility aid

If the patient is not discharged on day 3 ± 2,the patient should follow Danish Society of Orthopedic Surgeons (DSOS) guidelines (7 days). This group will be followed separately.

In case of regular treatment with acetylsalicylic acid or other thrombocyte inhibitor, this should be continued after surgery and with addition of thrombosisprophylaxis during hospitalization.

If the patient is in regular potent anticoagulative therapy (PACT), the patient will need bridging, with cessation of PACT 4 days preoperatively, and postoperative thrombosis prophylaxis until the patient's INR reaches therapeutic values (INR 2-3). This is done by the patients' general practitioner.

## 4. Statistics

A pre-study power-calculation showed that at least 3000 patients were needed (power(β) 82 % with a significance level (α) of 0,05) with expected event-rates of 3% (22-25)and a maximum event rate of 4 %. We expect to include about 5000 patients which would increase power and the statistic possibility of identifying risk-factors (preoperative variables). In addition isolated analysis on the primary procedures will be performed.

## 5. Budget

The study is partly financed by Århus University (1.100.000dkr)and the Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement(LCFHK) (550.000dkr). This has already been agreed upon.

Further project nurses/secretaries will be hired by LCFHK, therefore no further administrative assistance in relation to the project is expected.

There will be no pharmacological expenses.

Expenses in relation to transportation, travelling and course activities are expected to amount to about 50.000 dkr.

Data from the Danish National Patient Registry (NPR) about 15.000 dkr.

Other materials 5.000 dkr.

## 6. Safety analysis

To evaluate the risk of bleeding-complications in patients having THA or TKA in a fast-track setup (Appendix 2).

## 7. Duration of study

The expected duration of the study, assuming the aforementioned number of participants, is 24 months. All included patients will after 90 ±5 days be investigated by NPR. Duration of enrollment is estimated to be about 20 months. The study is expected to run from ultimo December ´09 until December ´11.

## 8. Interimanalysis

An interim analysis will be done after 1500 and 3000 patients.

Intention: To evaluate whether the true risk of complications is higher (worse treatment) or lower (better treatment) 4%. Three analyses will be done. In each analysis, the risk of complication including CI will be calculated. In the 1$^{st}$ analysis (1500 patients),the exact 99.5% CI will be calculated, in the 2$^{nd}$ analysis an exact 99 % CI and in the 3$^{rd}$ analysis (5000 pt) an exact 95.2% CI.

In simulation, it has been calculated that if the true risk is 3%, the total power is 97.6%. If the true risk of events is 6%, total power is 99.9%.

In case of an unacceptable safety profile and/or a very high number of primary events, the Clinical event committee can recommend an early termination of the study to the Steering committee, who will decide hereafter.

## 9. Data collection

After follow-up, data will be extracted from NPR with regards to diagnosis codes of vascular events, bleeding episodes, LOS and death. In case of events, the patient's medical charts will be requested and evaluated. The study is approved by the Danish Data Protection Agency.

## 10.Authors

According to alphabetical order, however, with writer as primary author and Henrik Kehlet as senior author. (13.1)

# 11.Study committees

The LCFHK will lead the logistic coordination of the different study committees.

## 11.1 Steering committee

The steering committee will ensure that all aspects of the study, such as safety and efficiency are maintained and that information from other committees can lead to timely changes.

Members:

Per Kjærsgaard-Andersen, Vejle Hospital

Torben Bæk Hansen, Regionshospitalet Holstebro

Henrik Husted, Hvidovre Hospital

Henrik Kehlet, Rigshospitalet, København

Mogens Berg Laursen, Ortopædkirurgien Nordjylland

Kjeld Søballe, Århus Universitetshospital

## 11.2 Clinical events committee

A clinical events committee will be founded, consisting of the writer and Steen Husted, where uncertainties regarding verification of diagnosis will be discussed. (Appendices 2+3)

# 12.Ethics and Legal aspects

## 12.1 Ethic Committee (EC)

The study will be presented to the Scientific Ethics Committee (SEC) and receive approval from here. It has been preliminarily approved as a quality-control study, as Hvidovre, Hørsholm and Farsø amongst others presently use this treatment as standard of care.

## 13.Ethical aspects and perspectives of the study

The duration of thrombosis prophylaxis after THA and TKA is subject to debate, both nationally and internationally. The degree of thrombo prophylactic effect vs. discomfort for the patient, bleeding-related side effects and, not the least, health related expenses need to be investigated in the "real life" setup in which the patients are operated. I Denmark the Danish Society of Orthopedic Surgeons recommend 7 days of treatment as a compromise (international recommendations up to 35 days), but also allow prolonged treatment on indication (unspecified). Studies suggest that with early mobilization and an uncomplicated postoperative phase the risk of VTE is significantly decreased. Thus there is no indication of prolonged thrombosis prophylaxis with related increased risk of bleeding-related side effects in this group(16). This study with short treatment thrombosis prophylaxis in patients having THA/TKA in a fast-track setup is in accordance with highest international expertise(17). Additionally there is disagreement regarding the American guidelines, where patients receive treatment with acetylsalicylic acid only(9).

We believe that this is a very important study, as it can influence, not only orthopedic recommendations, men generally on major surgery, such as abdominal surgery, gynecology, and other major surgical specialties using a fast-track setup(26;27). We believe that literature and, not in the least clinical experience, provide the background for a study of this character. Empirically, more and more surgeons do not follow the international recommendations and create their own. The Danish Society of Orthopedic Surgeons recommend 7 days of postoperative thrombosis prophylaxis (different from international recommendations), proving the lack of agreement in this area.

The design of the study will ensure that all data and the analysis of data will be in accordance with the Helsinki Declaration as well as local laws and regulations. The investigators will at any point allow the Steering committee or representatives of the Steering committee to review documents in order to ensure this.

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Ref Type: Electronic Citation

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# 15.Appendix 1

## Local postoperative prophylaxis guidelines:

ÅrhusSygehus: LMWH (Arixtra) for 7 daysin THA/ 5-7 daysFragminin TKA.

Holstebro: LMWH (Fragmin) in 7 daysin THA/TKA.

Hvidovre: $X_{10a}$ (Xarelto) 10 mg to discharge in THA/TKA.

Ortopædkirurgien Nordjylland: LMWH (Fragmin) to discharge THA/TKA

Vejle: LMWH (Klexane) for 7 days in THA/TKA

Sydvestjysk Sygehus Grindsted: LMWH (Arixtra) 2.5mg x1 for 7 days in THA/TKA

# 16.Appendix 2

## Bleeding

The safety endpoint is the frequency of bleeding(28)observe red no later than 2 days after last administration of thrombosis prophylaxis. Bleeding more than 2 days after last dose of thrombosis prophylaxis will not be considered as a side-effect.

**Diagnosis of bleeding**

In case of bleeding all information, ie. Anesthesia-charts, laboratory results, ultrasound findings, must be registered in the medical chart. All bleeding-episodes will be classified according to predefined criteria:

Serious bleeding

Minor bleedings

**Serious Bleedings are:**

- Fatal bleeding
- Bleeding in a critical organ(retroperitoneal, intracraniel, intraocular, intraspinal, pericardiac bleeding with tamponade, intramuscular bleeding with compartment syndrome)
- Bleeding needing surgical intervention (including joint puncture and aspiration)
- Bleeding leading to infusion of >1 portion of SAGM/full blood
- Bleeding index ≥2 (defined as number of transfused portions of erythrocytes + diff between hemoglobin before and after bleeding measured in gram/dl).
- Drop in hemoglobin of > 30g/L (=1,9mmol/L)
- **All bleedings not classified as serious bleedings will be classified as minor bleedings**

# 17.Appendix 3

Definition of clinical outcomes:

## 17.1 DVT

Diagnosis done by ultrasound (if not possible venography). The main criteria for DVT is a negative compression test with ultrasound(9).

## 17.2 Pulmonary embolism

Diagnosed by

- Spiral CT-scan (29)
- Perfusion-ventilation scintigrafia(9)
- Pathologicalremoval of embolus(9)

## 17.3 Myocardial infarction

Diagnosed in the following situations(30)

- Increase and/or fall in specific biomarkers (mainly troponin) with at least 1 value higher than the 99 percentile of upper reference threshold and

  Evidence for myocardial ischemia with at leastone of the following:

  - Symptoms of ischemia ( chest pain, dyspnoea, acute heart failure, arrhythmia)

  - ECG changes indicative of acute ischemia (new ST-T changes or new left side bundle branch block)

  - Development of pathological Q-waves on ECG

  - Radiological diagnostic evidence of new loss of viable myocardium or new regional dyskinesia.

  - Revasculisation by PCI or CABG.

## 17.4 Stroke

Defined as an acute neurological event with focal neurologic deficits and duration beyond 24 hours (31), verified by CT/MR-scan. Strokes will be stratified according to type as ischemic, hemorrhagic or unknown.

In case of progression of formerly known neurological symptoms, the progression must be present for more than 1 week or 24 hours if accompanied by new relevant CT or MR findings.

### Cardiovascular death

Death of vascular causes include cardiovascular, cerebrovascular and death of other vascular causes or death with no clear documentation of non-vascular cause. Ex:

Vascular death: Sudden death, MI, unstable angina pectoris, other CAD, stroke, arterial embolism, pulmonary embolism, dissecting aorta, heart insufficiency, cardiac arrhythmia, or death from bleeding (non-trauma related)

Non-vascular death: Respiratory failure, pneumonia, cancer, trauma, suicide or other defined cause (i.e. liver or renal failure)

Death of unknown /uncertain causes will be categorized as vascular death.

**TCI**

Definition is as for stroke, but are temporary and gone <24 hours.

## 17.5 Other thromboembolic events

Need to be defined by a relevant specialist.

# 18.Appendix 4

Date of surgery
Social security number

Joint (knee/hip)

Height: _____ cm

Weight: _____kg

Hemoglobin level _____ mmol/l
(Taken no more than 1 week previously)
Patients' blood type?

Living conditions (alone, with spouse/others, in institution (nursing home etc.)
Smoking (yes/no)
Alcohol >2 units a day (yes/no)
Do you use walking aids prior to admission?
Are you feeling well rested in the morning?
Do you snore loudly?
Do you use compressive stockings regularly?

Do you receive treatment for high cholesterol (yes/no)
Do you receive treatment for high blood pressure (yes/no)
Do you have Type 1 diabetes (yes/no)
Do you have Type 2 diabetes (yes/no)
Have you had a previous cerebral attack?
Have you had a previous venous thromboembolic event?
Do you receive medication for any type of heart disease?
Do you receive medication for any type of pulmonary disease?
Do you receive medication for any type of psychiatric disease?
Do you have a family member who has had a deep venous thrombosis or pulmonary embolus?
Do you have a contraindication for antithrombotic medication?

Do you use antithrombotic medication regularly (marevan, acetyl salicylic acid etc)?

# 19.Protocol editing and changes after study initiation

1) **Project leader and coordinating investigator:** Changed from Michael Kjær Jacobsen to Christoffer C. Jørgensen
2) **Other investigators:** The following investigators have been removed as the study was not initiated at their institutions: Steen Husted MD, Århus Universitety Hospital, THG Århus, Søren Mikkelsen MD, Regionshospitalet Silkeborg.
   The following investigators have been edited: Søren Solgaard MD, Gentofte Hospital Gentofte.
   The following investigators have been added: Lars Tambour Hansen MD, Sydvestjysk Sygehus Grindsted/Esbjerg
3) **Statistician:** Niels Trolle Andersen is no longer responsible for statistics. Christoffer C. Jørgensen has been added and additional assistance will be acquired as needed.
4) **Study sites:**The following study sites have not participated: Regionshospitalet Silkeborg, Hørsholm Hospital (due to closure). The following study sites have been added: Sydvestjysk Hospital Grindsted/Esbjerg April 2010, Gentofte Hospital, November 2012.
5) **Background:** Hørsholm Hospital has been mentioned as having used short-treatment prophylaxis as standard of care. This is a mistake and should be omitted.
6) **2.1 Design:** Due to a large number of available patients, it has been decided to expand the study size. The intention is now to include 5000 PRIMARY operations in addition to a number of revisions and uni-KA. 3.
7) **3. Patient selection:** Changes according to 4) **Study sites**.
8) **3.3 Discharge criteria:** Thrombosis prophylaxis in patients with LOS >5 days: DOS guidelines are not 7 days, but 5-10 days in TKA and 7-35 days after THA.
9) **4. Statistics:** The exact number of patients when using a Two-tailed one sample difference from constant test with the in the protocol mentioned specifications is 2838. Using the same test, 2076 patients will be needed to detect a 1% increase in frequency of symptomatic VTE, using $\alpha$: 0.05, $\beta$: 82 and a baseline risk of 1% with 35 days of treatment with LMWH.
10) **7. Duration of study:** As the database of this study forms the core of several independent studies on co-morbidity, duration of this study has been extended, and database registration is expected to last until ultimo 2016
11) **9. Data collection:** Collection of data has been changed from depending on ICD-10 diagnostic codes for vascular events only to include ALL readmissions in 90 days. These will be investigated using discharge papers and complete medical charts in order to increase quality of data. In addition further details on regular anti-coagulative therapy 6 months prior to surgery and 3 months after surgery be collected through a newly established cooperation with the Danish National Database of Reimbursed Prescriptions, in order to further improve data quality.[1]
12) **10. Authors:** Christoffer Calov Jørgensen is now primary author, Michael Kjær Jacobsen will figure as secondary author and Henrik Kehlet as senior author. The remaining investigators are co-authors in a random order when patients from their study sites are included in the specific studies.
13) **11.1 Steering committee:** The following persons are not part of the steering committee: Steen Husted, Lars-Peter Jorn, Søren Mikkelsen, Søren Solgaard.
14) **11.2 Clinical event Committee:** Consists of Christoffer Calov Jørgensen and Henrik Kehlet.
15) **12.1 Ethic Committee:** The study ended up being considered as a quality-control study on a standard of care. The Scientific Ethics Committee decided that the study needed no approval.
16) **Appendix 1:** The local prophylaxis guidelines of the following departments are not relevant: Hørsholm and Silkeborg. Guidelines for the added departments are: Gentofte Hospital: $X_{10a}$ inhibitor (Xarelto) 10 mg x 1 in both THA/TKA until discharge. Sydvestjysk Sygehus Grindsted: LMWH (Arixtra) 2.5mg x 1 for 7 days. Treatment has been changed after study initiation in the

following departments: Hvidovre Hospital: $X_{10a}$ inhibitor (Xarelto) 10 mg to discharge THA/TKA. Viborg Hospital: LMWH (Fragmin) 5000 ie x 1 for 10 days.

[1]Johannesdottir SA, Horváth-Puhó E, Schmidt M, Ehrenstein V, Pedersen L, Sørensen HT. Existing data sources for clinical epidemiology:The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012;4:1-11.