FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

PhD thesis

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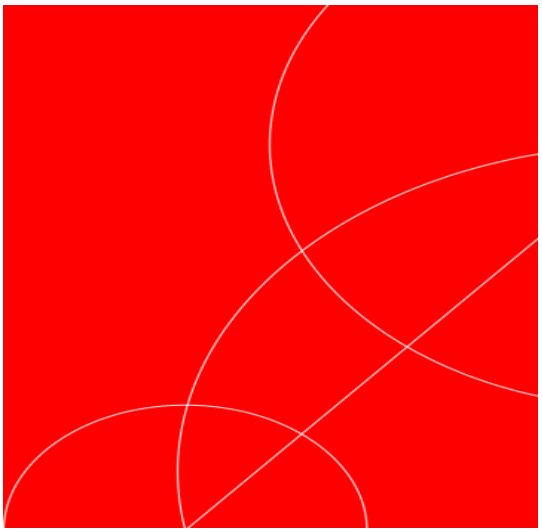
Blood Loss in Hip Fractures

Results of four clinical trials



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Thank you!

To my wife for your love and patience
To my daughters for your happiness
To my supervisors for their insight and pragmatism
To the head of my department for never turning down a good idea
To my colleagues for good advice, moral support and good humor

Blood Loss in Hip-fractures

List of Papers

I. Tranexamic Acid (TXA) reduces blood loss in patients with extra-capsular hip-fractures; results of a randomized controlled trial.
Peter Toft Tengberg MD*; Henrik Palm MD*; Nicolai Bang Foss MD, DMSc**; Thomas Kallemose MSc*,‡; Anders Troelsen MD Ph.d. DMSc Professor*.
Submitted manuscript

II. Hip-Fracture Surgery on patients in Clopidogrel therapy is not associated with high risk of major blood loss. A retrospective observational study.
Peter Toft Tengberg MD*; Lisa Lethan MD*; Henrik Palm MD*; Nicolai Bang Foss MD, DMSc**; Thomas Kallemose MSc*,‡; Anders Troelsen MD Ph.d. DMSc Professor*.
Submitted manuscript

III. The case for continuing Clopidogrel® therapy during hip-fracture surgery. Results of a systematic review.
Peter Toft Tengberg MD*; Ann Ganestam MD*; Henrik Palm MD*; Nicolai Bang Foss MD, DMSc**; Thomas Kallemose MSc*,‡; Anders Troelsen MD Ph.d. DMSc Professor*.
Submitted manuscript

IV. Low incidence of pre-operative coagulopathies measured by Thrombelastography® (TEG®) in hip-fracture patients. A prospective observational study.
Peter Toft Tengberg MD*; Henrik Palm MD*; Nicolai Bang Foss MD, DMSc**;Thomas Kallemose MSc*,‡; Anders Troelsen MD Ph.d. DMSc Professor*.

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Abbreviations

SBL = Surgical Blood Loss
TBL = Total Blood Loss
ASA = Acetylsalicylic Acid
VKA = Vitamin K Antagonists
PAI = Platelet Aggregation Inhibitors
PT = Prothrombin Time
aPTT = activated Partial Thromboplastin Time
IMN = Intramedullary Nail
DAPT = Dual Antiplatelet Therapy
SBE = Surgical Bleeding Event
INR = International Normalized Ratio
VHA = Viscoelastic Haemostatic Assay
TEG = Thrombelastography®
PANT = Postoperative Anaemia Necessitating Transfusion
TXA = Tranexamic Acid
RBC = Red Blood Cell (transfusions)
TE = Thromboembolic Event(s)

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Dansk resumé

Kære læser, dette er det kondenserede resultat af tre og et halvt års intenst arbejde. Emnet for denne tese er flere forskellige aspekter af blodtab hos hoftefraktur patienter. For at lette læsningen for dig har jeg lavet en kort tabel der sammenfatter de fire studier i tesens; spørgsmål, metode, design og svar nedenfor.

Studie	Spørgsmål	Metode	Design	Svar
I	**Reducerer Tranexamsyre (TXA) blodtabet hos hoftefraktur patienter?**	Ekstra kapsulære frakturer ± TXA	Dobbelt blindet RCT	**Ja**
II	**Er Clopidogrel behandling i forbindelse med hoftefraktur kirurgi forbundet med høj risiko for blødning?**	Ekstra kapsulære frakturer ± Clopidogrel	Retrospektivt observationsstudie	**Nej**
III	**Er Clopidogrel behandling i forbindelse med hoftefraktur kirurgi forbundet med høj risiko for blødning?**	Alle typer hoftefrakturer ± Clopidogrel	Systematisk review og meta-analysis	**Nej**
IVa	**Kan TEG analyse ved indlæggelse forudsige hvilke patienter der er i risiko for store blodtab?**	Alle typer hoftefrakturer + TEG ved indlæggelse	Deskriptivt, prospektivt observationsstudie	**Nej**
IVb	**Er der en høj forekomst af koagulopatier målt af TEG ved indlæggelse hos hoftefraktur patienter?**	Alle typer hoftefrakturer + TEG ved indlæggelse	Deskriptivt, prospektivt observationsstudie	**Nej**

God læselyst.

English summary

Dear reader, you are holding a copy of the condensed results of three and a half intense years of work. The subject of this thesis is different aspects of blood loss in hip-fracture patients. To ease the reading for you I have provided you with a brief summary of the research questions, methods, design and answers in a table below.

Study	Question	Methods	Design	Answer
I	**Does TXA reduce the TBL in hip-fracture patients?**	Extra-capsular Hip-fracture ± TXA	Double-blinded RCT	**Yes**
II	**Is Clopidogrel treatment during hip-fracture surgery associated with high risk of bleeding?**	Extra-capsular hip-fracture ± Clopidogrel	Retrospective observational study	**No**
III	**Is Clopidogrel treatment during hip-fracture surgery associated with high risk of bleeding?**	All types of hip-fractures ± Clopidogrel	Systematic review and meta-analysis	**No**
IVa	**Can on-admission TEG predict patients at risk for large blood loss in hip-fracture patients?**	All types of hip-fractures + TEG on-admission	Descriptive, prospective observational study	**No**
IVb	**Is there a high prevalence of coagulopathies as measured by TEG on-admission in hip-fracture patients?**	All types of hip-fractures + TEG on-admission	Descriptive, prospective observational study	**No**

Enjoy your reading.

1 Introduction

Since the dawn of surgery, surgical bleeding has been a problem for surgeons and even more so for the patients. Galen was allegedly the first surgeon to experiment with methods to reduce bleeding through the method of ligating arteries on live animals. Ambroise Paré reintroduced this method much later to replace the method of cauterization to stop bleeding from amputations. The technical measures used by the surgeon still plays a pivotal part in the reduction of blood loss from surgery. But many other factors influence the magnitude of the blood loss both before, during and after surgery.

2 Hip-fractures

The incidence of hip-fractures is on the rise and is expected to near 6 million worldwide by the year 2050. With in-hospital mortalities between 7-14% and a 1-year mortality at a staggering 14-36%. Mortality has remained unchanged through four decades, despite changes in treatment [1–3].

The prevalence of hip-fractures in Denmark is approximately 10,000 a year, thereby accounting for 2.2 % of total patient bed days [4]. The hip-fracture patient is often elderly and fragile with multiple co-morbidities. They pose a challenge to all medical staff involved,

and there is a great potential for improving the treatment, which would benefit patients and society alike [4,5].

3 Blood Loss

The loss of blood through haemorrhage leads to hypovolemia which in turn leads to tachycardia and a decrease in systolic blood pressure [6–9]. The decreased blood volume and lowered blood pressure leads to a decreased organ perfusion which may cause organ failure and ultimately death [10].
Blood loss can be categorized in different ways relating to its cause. In this paper we use two different methods and also the indirect measure of RBC transfusions.

3.1 Surgical Blood Loss (SBL)

All surgery is associated with blood loss. The Surgical Blood Loss (SBL) is the immediately visible/measurable blood loss that occurs during surgery.

3.2 Total Blood Loss (TBL)

Hip-fractures are associated with a large Total Blood Loss (TBL). This blood loss is much greater than that observed intra operatively. The TBL depends on the type of fracture and associated surgery. Extra-capsular fractures treated with an intramedullary nail are thus associated with the largest TBL with a median of approximately 1500 ml [11]. The majority of the TBL has been suggested to be associated with the trauma and fracture itself and not, as such, with the surgical procedure [12].
TBL is calculated based on patient gender; weight; height; haemoglobin measurements on admission(Hgb_{adm}) and on the third day after surgery (Hgb_{fin}); and number of transfusions (*55 grams of haemoglobin per unit*). These variables are used to calculate the blood volume of the patient using Nadlers[13] formula for blood volume:

$$Womens\ Blood\ volume\ \ l\ \ = height\ (m)^3\ \times 0.356 + weight\ \ \ kg\ \ \times 0.033 + 0.183$$

$$Mens\ Blood\ volume\ \ l\ \ = height\ (m)^3\ \times 0.356 + weight\ \ \ kg\ \ \times 0.032 + 0.604$$

The blood volume of the patient is then used to calculate the amount of haemoglobin lost (Hgb_{loss}) from admission to the third postoperative day [14,15]:

$$Hgb_{loss}\ \ g\ \ = Blood\ volume\ (l)\ \times\ \ Hgb_{adm}\ \ g/l\ \ - Hgb_{fin}\ \ g/l\ \ \ + Hgb_{trans}(g)$$

The haemoglobin loss is then converted to a volume loss:

$$TBL\ \ \ ml\ \ = (Hgb_{loss}(g)/Hgb_{adm}(g/l) \times 1000$$

3.3 RBC Transfusion

Blood loss is often replaced by RBC transfusions. This is subject to variation according to tradition and department standards. Our departments transfusions threshold is < 6mmol/l (10 g/dl) of haemoglobin.

4 Coagulation

4.1 Coagulation cascade or "the cell based model"

When a haemorrhage occurs from a blood vessel the body responds almost immediately by causing haemostasis of the vessel through activation of the complex coagulation cascade, explained by the cell-based model. The damage to a vessel exposes the blood to the tissue under the endothelium that contains collagen, von Willebrand Factor and tissue factor. Circulating platelets adhere directly to the exposed collagen, creating a plug in the damaged vessel. This plug is strengthened through links formed by von Willebrand Factor. Circulating Factor VII is activated when it comes into contact with tissue factor thereby activating the coagulation cascade that leads to a stabilised cross linked fibrin clot [16,17].

4.2 Coagulation tests

A large array of tests to assess patient coagulation and the presence of coagulopathies exists.

4.2.1 Conventional Coagulation Tests

Prothrombin Time (PT); activated Partial Thromboplastin Time (aPTT) and International Normalized Ratio (INR) are among the frequently used tests to assess the presence of coagulopathies. But these tests were designed to monitor haemophilia and anticoagulation therapy and are not validated for the prediction of haemorrhagic tendency in a clinical setting [18–20].

4.2.2 Viscoelastic Haemostatic Assays

Thrombelastography® (TEG) was introduced in 1948 [21]. It is a whole blood coagulation analysis that imitates sluggish venous flow. It is performed by suspending a blood sample in a small cup that is rotated while a sensor shaft is inserted. A blood clot forms between the wall of the cup and the sensor shaft. Measurements are provided as a graph. It provides the clinician with an evaluation of the kinetics of all stages of coagulation from clot initiation to breakdown [20,22,23]. Traditionally presented as five different values that represent these stages:

- R: represents the reaction time to initiation of clot formation
- K: kinetics of clot formation
- α-angle: the slope between R and K
- MA: Maximum Amplitude that represents clot strength
- LY30: Amplitude reduction 30 min. after MA. Represents lysis of the clot.

TEG and other types of VHA (Rotation Thrombelastometry®) are being used to detect coagulopathies and guide transfusion therapy in patients with massive blood loss (liver-, cardiac- and trauma-surgery). They have shown a positive effect on the use blood products, but there is a lack of evidence on its effect on morbidity and mortality when comparing VHA based algorithms to standard treatment [22–24].

5 Factors Influencing Blood Loss

Several factors influence the blood loss of a hip-fracture patient.

5.1 Inherent factors

Patients may have hereditary or acquired conditions that affect their coagulation, such as von Willebrand disease, haemophilia, liver disease, kidney disease or a number of other conditions that directly or indirectly affect the patients´ ability to create haemostasis.

5.2 Coagulopathy

Coagulopathies may be induced by several different factors, including trauma; surgery; infection; acidosis; hypothermia; hypocalcaemia and other factors such as dilution and anaemia [18,25]. All of these factors may cause some degree of coagulopathy. Severe cases of trauma-induced coagulopathy can cause very large blood losses and are associated with an increased mortality [26–29].

5.3 Medication

Several anticoagulation and antiplatelet medicines increase the blood loss in surgical patients. Acetylsalicylic acid (ASA), Vitamin K Antagonists (VKA), Platelet Aggregation Inhibitors (PAI), Factor Xa inhibitors and several other similar drugs all increase the blood loss to some extent during surgery [30,31].

5.4 Fracture type and surgery

Type of fracture, surgical technique and blood pressure of the patient during surgery also influence the blood loss during and after hip-fracture surgery [11].

6 Preventive measures

Traditional measures to prevent blood loss in hip-fracture patients include pre-operative reversal of anticoagulation medicine, pre- or per-operative administration of relevant component therapy (Platelets, Fresh Frozen Plasma (FFP)) and the use of haemostatic drugs such as Tranexamic Acid (TXA) [32]. Other measures include meticulous surgical technique with coagulation of damaged vessels and proper skin closure.

7 Transfusions

Red Blood Cell (RBC)-transfusions are used to replace blood loss in surgical patients, including hip-fracture patients. Controversy exists as to the optimal transfusion threshold and some researchers suggest that a liberal transfusion strategy may cause an increase in morbidity and even mortality [33,34]. This argumentation is limited by the bias by indication for an RBC-transfusion. This has led to the coining of the term Postoperative Anaemia Necessitating Transfusion (PANT) which, together with pre-operative anaemia, has been shown to be an independent risk factor for a worsened outcome in hip fracture patients [35]. Several studies have shown that a liberal transfusion strategy for hip fracture patients is not associated with increased morbidity or mortality [36] and some studies have found that it benefits the hip-fracture patient by decreasing the time to ambulation and length of stay [37,38].

8 Aims

8.1 Thesis

The aim of this thesis was to investigate the effect of different measures to reduce the blood loss in hip-fracture patients and to evaluate the effect of antiplatelet medicine on blood loss in these patients.

8.2 Study I: "Tranexamic Acid (TXA) reduces blood loss in patients with extra-capsular hip-fractures; results of a randomized controlled trial"

The aim of this single-center placebo-controlled double-blinded randomized clinical trial was to investigate if the administration of TXA pre- and post-operatively could reduce TBL, SBL and number of RBC-transfusions in extra-capsular hip-fractures.

8.3 Study II: "Hip-Fracture Surgery on patients in Clopidogrel therapy is not associated with high risk of major blood loss. A retrospective observational study."

The aim of this retrospective observational study was to investigate the difference in blood loss (Evaluated as: SBL, TBL, RBC transfusions and occurrences of Massive Transfusion/occurrences of irreversible, uncontrollable blood loss) between patients undergoing surgery for extra-capsular hip-fractures in Clopidogrel therapy compared to patients who are not in any form of anticoagulation therapy.

8.4 Study III: "The case for continuing Clopidogrel® therapy during hip-fracture surgery. Results of a systematic review."

The aim of this systematic review of the English literature was to ascertain if it is safe to perform hip-fracture surgery on patients that are not discontinued in Clopidogrel therapy before surgery.

8.5 Study IV: "Low incidence of pre-operative coagulopathies measured by Thrombelastography® (TEG®) in hip-fracture patients."

The aim of this blinded prospective observational study was to investigate the incidence of coagulopathies on admission in patients with hip-fractures. We also investigated the correlation between on-admission TEG values and TBL.

9 Outcome Assessment

Here follows a critical appraisal of all outcome measures grouped according to type.

9.1 Blood Loss related outcomes

All studies use blood loss in some form as an outcome measure.

9.1.1 Surgical Blood Loss (SBL)

The value of SBL as an outcome parameter must be regarded critically. The problem with the outcome is that SBL can be reported in several ways and none of them are very accurate [39]:

- **Visual assessment:** This is probably the most frequently but also the most inaccurate method. Especially large blood loss is subject to gross estimation error. This method alone is not recommended for research outcomes.

- **Direct measurement:** Blood lost during the procedure is collected in suction drains and collection bags in the draping and measured directly. This method still requires some estimation of blood on the floor, draping, surgeons´ gown and instruments.
- **Weighing (Gravimetric):** The weighing of tissues, swabs and other blood stained cloth used in the procedure. This method does not account for other fluids such as water used during the procedure.

In our studies we have used the department standard which is a combination of the three methods mentioned above. The accuracy of the outcome is debateable, but in **Study II** where SBL is the primary outcome the aim was not to identify small differences in SBL between the Clopidogrel and control group, but rather to exclude the presence of large differences. The errors of measurement must be assumed to be equal in the two groups. The method of measurement represents the actual clinical situation in most hospitals, which gives the study high external validity.

9.1.2 Total Blood Loss (TBL)

TBL is a compound outcome used in several studies of orthopaedic patients, where it is called the Hidden Blood Loss (which equals the TBL minus the measured blood loos (SBL)) [11,14,15,40–42]. This method has been validated in a study of blood donors [43] which found that the method underestimates the blood loss. The study concludes that the method is not suitable for an absolute measure of the blood loss volume but is well suited for a rough estimate.
The calculation of TBL is done by the formulas as outlined in section 3.2 above.
The formulae are dependent on several variables:

- **Weight and Height:** These are based on estimates by the admitting doctor and the patients´ own account. An error of estimate of ± 1 kg bodyweight equals ± 33 ml of blood volume and an error of estimate of ± 1 cm equals ± 27 ml in a female patient.
- **Blood volume:** Calculated by Nadler´s formula[13]. TBL is calculated as a function of blood volume so changes in blood volume by error of estimation of height and weight impacts the TBL calculation.
- **Haemoglobin measurements:** TBL calculation depends on haemoglobin measurements. It is assumed that the blood volume after an acute blood loss is rapidly restored by redistribution of extravascular fluid to the intravascular space, which leads to a dilution of haemoglobin. This allows us to use haemoglobin concentration before and after blood loss to calculate the TBL.
  These are made on admission and the three days following surgery. A study on blood donors have shown that haemoglobin continues to decrease until six days after the moderate (450 ml) blood loss. This rise in haemoglobin at day six is probably attributable to erythropoiesis. This interferes with the calculation of the blood loss. The study also showed that the earlier the haemoglobin is measured in relation to the blood loss, the larger is the underestimation [43].
- **RBC Transfusions:** The amount of transfused haemoglobin (55 g per Unit of RBC) is added to the TBL. Threshold for transfusion is < 6 mmol/l (10 g/dl) in our department. Haemoglobin measurements that may trigger a transfusion are done once daily in the first three days after operation.

TBL is the primary outcome in **Study I**, and secondary outcomes in **Study II** and **Study IV**. This outcome is not an exact measure, but if anything, it underestimates the actual blood

loss. The outcome is used in **Study I and II** to assess differences between two groups. The errors are assumed to occur with equal frequency in the two groups (systematic error) and the exactness of the estimate is therefore not important. In **Study IV** it is used as a rough estimate of the blood loss.

9.1.3 RBC Transfusion

Transfusion is used as an indirect outcome measure of blood loss in all four studies. This outcome depends on the transfusion threshold in the department and also on the frequency of haemoglobin measurements. **Study I, II** and **IV** were all conducted in our department that has a standardized setup. Blood samples are taken on daily morning rounds the first three postoperative days. Transfusion threshold is <6 mmol/l (10 g/dl). In **Study III** we found heterogeneity in threshold and frequency of blood samples and were therefore not able to compare the studies regarding transfusion as an outcome.

9.1.4 Massive transfusion

The three most common definitions of massive transfusion are [44]:

1. **Transfusion of ≥10 Units of RBC in <24 hours.**
2. Transfusion of >4 Units of RBC in 1 hour, continued need anticipated.
3. Replacement of >50% of the total blood volume by blood products within 3 hours.

In **Study II** we used the first definition as a secondary outcome. We did not have sufficient data to use the two other definitions. The outcome was relevant **Study II** were we tried to ascertain the risks of surgery on patients under the effect of Clopidogrel treatment. One of the theoretical risks is an uncontrollable and irreversible bleeding during surgery. This would result in massive transfusion and we therefore included it in the study. The data used for this endpoint are the number of transfusions. The validity of these data is very high as the number of transfusions is meticulously recorded in the hospital blood bank.

9.1.5 Surgical Bleeding Events (SBE)

In **Study II** and **III** we used this outcome. It is a combination of haematoma and wound discharge postoperatively. In **Study III** we reported this outcome based on the reports in the papers. In **Study II** we reported the outcome based on reports in patient charts. As a retrospective outcome it is probably very biased. Even in a prospective setup it can be very hard to define. The outcome measure itself is therefore not very good to make inferences on.

9.1.6 Re-operation due to SBE

This outcome was also reported in **Study II** and **III**. This is a more clinically relevant outcome and it is probably much less biased than the SBE outcome itself. The relatively rare case of reoperation is almost always reported and labelled with some indication for the reoperation. The agreement between actual indication and reported indication is thought to be high.

9.1.7 Reported incidents of uncontrollable bleeding during or after surgery

This outcome is reported in **Study III**. It is not a very well-defined outcome but it is considered relevant in the context of the review where we investigate the potential hazards of performing hip-fracture surgery on patients in Clopidogrel therapy. The outcome is

reported based on reports in the papers included in the review. The outcome is not reported in any of these studies, but all studies were done with a focus on bleeding complications. If the outcome had occurred in any of the studies we feel confident that it would have been reported.

9.2 Mortality

All studies use mortality as an outcome.

9.2.1 30 and 90 day (all-cause) mortality

Mortality (all-cause) is a compound outcome with almost infinite possibilities of cause. We only used short-term mortality as an outcome in our studies because the intervention in each study was not thought to affect long-term mortality.
None of our studies were powered to make inferences on mortality.
We were not able to gain information on cause of death in any of our studies.
In **Study I** that investigates the effect of TXA in hip-fracture patients, this could mean that we are underreporting the incidence of Thromboembolic Events (TE) in the cases where it leads to immediate death.
In **Study II** it is harder to imagine that a cause of death attributable to massive bleeding during or after surgery would be overlooked and not reported in the patient charts.
The same goes for the reviewed papers in **Study III** where such events would most likely be reported.
The usefulness of 90-day mortality as an outcome in **Study IV** is debateable due to the relatively small study population and we did not hypothesize that this outcome would show any significance in relation to the four reported TEG variables, but we felt it was important to report as a study of this kind never had been conducted before. Hypocoagulability measured by TEG have been related to 30 day mortality, but this was in an ICU setting where the incidence of hypocoagulability is much higher [26].

The overall usefulness of 30 and 90 day mortality should be seen in the context of the problems with establishing the true cause of death in this population (and other study populations). Attempts at gaining causes for mortality in a study population would always be subject to a number of possible errors, thereby biasing the conclusion. Therefore all-cause mortality is probably the most useful outcome in these types of studies.

9.3 Thromboembolic Events (TE)

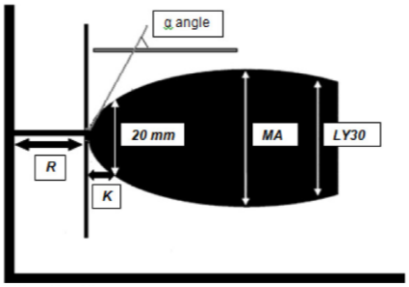
9.3.1 90 day incidence of TE

Study I uses this as a safety outcome. The study is not powered to make inferences on this outcome. The quality of this outcome measure is questionable as already mentioned under *9.2 Mortality*. We only reported TE´s that lead to re-admission in a Danish hospital. We did not conduct routine ultrasound evaluation for TE´s in our population. We were not able to ascertain if TE was the direct cause of death in any of our patients.

9.4 TEG variables

We used the four clinically relevant TEG variables (R, MA, Angle and LY30) as outcome measures related to TBL in **Study IV**. The theory behind this was that several studies have shown the usefulness of TEG to identify trauma-induced coagulopathies [20,24,26]. We

hypothesized that the frail patients group of hip-fracture patients would respond to fractures in a similar, though probably less dramatic, manner.



Schematic representation of TEG plot (By: Luis Teodoro da Luz, Bartolomeu Nascimento, and Sandro Rizoli)

9.4.1 R

The variable R (given in min.) depicts the reaction time, i.e. the time to the first detectable evidence of clot formation.

9.4.2 MA

The variable MA (given in mm.) depicts the Maximal Amplitude and represents the strength of the clot.

9.4.3 Angle

The Angle (or α-angle) is the tangent of the curve made as K is reached. It represents the speed of the clot formation i.e. a steep angle means that the clot forms quickly and vice-versa.

9.4.4 LY30

This value (given as a percentage) represents the percentage the clot which has dissolved (lysis) after 30 minutes.

9.4.5 Normal values of TEG variables

In **Study IV** we report the number of TEG variables outside normal range. This was done to ascertain the usefulness of TEG as an on admission screening test for coagulation disorders in hip-fracture patients. This outcome is clinically relevant and has high external validity as it was performed on almost 200 consecutive hip-fracture patients with almost no exclusion criteria.

9.4.6 Prediction model for TBL based on TEG variables

In **Study IV** we tested the ability of TEG taken on admission to predict the overall TBL in hip-fracture patients. There are several problems pertaining to this outcome. First of all blood loss is a compound outcome influenced by numerous factors that TEG cannot predict. Secondly we only measured TEG on admission and we could therefore not make any inferences on the impact on coagulation made by the “trauma” of the surgery. We can only make inferences on the value of TEG taken immediately after admission.

10 Subjects and Methods

All four studies were conducted on hip-fracture patients who were treated according to the standardized regime at our department [45].

10.1 The "Hvidovre Algorithm" and standardized treatment

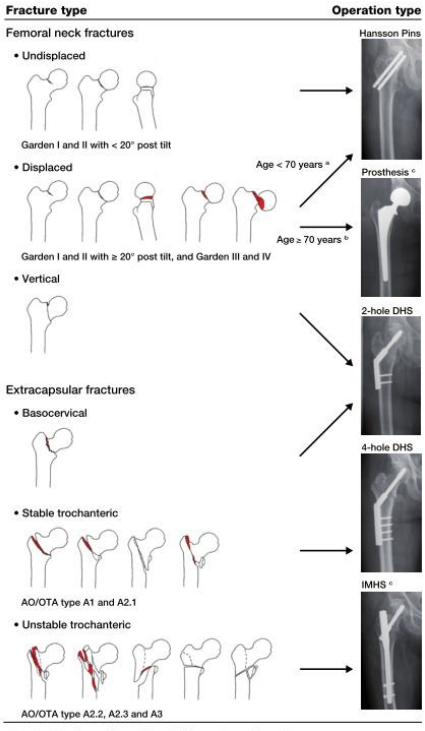
At Hvidovre Hospital all hip-fracture patients are treated according to a standardized regime. This includes:

Pre-operative:

- **Admission to a dedicated hip-fracture ward.**
- **Standardized blood work-up, including daily haemoglobin measurements.**
- **Epidural catheter for pain relief and anaesthesia during operation**
- **Liberal transfusion trigger at 6.0 mmol/l (~10 g/dl)**
- **Operation within 24-36 hours**

Operation

- **All patients are operated according to a standardized algorithm**.



The algorithm for hip fracture surgery.

Postoperative

- **Admission to a dedicated hip-fracture ward.**
- **Standardized fluid regime (1500-2000 ml intake daily)**
- **5000 IE of LMWH at 10 pm. daily.**
- **Postoperative mobilization from day one.**
- **Postoperative epidural analgesia for pain relief.**

10.2 General considerations

10.2.1 Hip fractures and blood loss

There are some general considerations when it comes to hip-fractures and blood loss. There are two categories of hip-fractures. Intra-capsular and extra-capsular. Each of these have several subdivisions. The type of fracture impacts the blood loss [11,12].
The extra-capsular fractures are characterized by a large blood loss, probably because they have a large bone surfaces that can bleed into a big compartment. The type of operation probably also impacts the blood loss.
The intra-capsular fractures on the other hand have smaller bone surfaces and most often bleed into the closed compartment of the capsule. The type of operation chosen for the intra-capsular fractures also impact the blood loss as a hemiarthroplasty, needless to say, bleeds more than a pair of parallel screws. This has affected our choice of study population in **Study I** and **II**.

10.2.2 Target population

The target population is the population a researcher seeks to make inferences on.

10.2.3 Study population

The study population is the population that the researcher actually investigated in the study. Ideally the target and study population are identical, but this is rarely the case.

10.3 Study I: Tranexamic Acid (TXA) reduces blood loss in patients with extra-capsular hip-fractures; results of a randomized controlled trial.

10.3.1 Study design

The study was conducted as a single-centre placebo-controlled double-blinded randomized clinical trial. The study was performed and reported in accordance with the CONSORT statement [46]. We compared the effect on TBL of administration of TXA pre- and post-operatively with a similar regime using placebo.

10.3.2 Target population

Our target population was all categories of hip-fracture patients who were eligible to receive TXA.

10.3.3 Study population

Our subjects were all patients treated for an extra-capsular fracture with an intramedullary nail (IMN). This study population was chosen as it has the greatest blood loss [11]. We would therefore need fewer subjects to show a clinically significant effect of the treatment. We chose some strict exclusion criteria for the study, including s-creatinine >120 µmol/l. TXA can be used in patients with s-creatinine >500 µmol/l if proper adjustments to dose is made. The study population therefore does not match the target population exactly but we still feel confident that inferences from the study can be applied to all hip-fracture patients. The differences between study and target population will not affect the effect or safety of TXA as long as the instructions regarding use in patients with elevated s-creatinine provided by the manufacturer is followed.

10.3.4 Material

All patients in the study were treated according to department standards. In addition to this study patients were treated according to their randomly assigned group:

Intervention: Patients were given a bolus of 1 gram of TXA prior to surgery, during draping. After surgery they were given 3 grams of TXA in 1 litre of saline in a 24 hour drip.
Control: Patients were given a bolus of saline prior to surgery, during draping. After surgery they were given 1 litre of saline in a 24 hour drip.

10.3.5 Ethical considerations
TXA is a time-tested drug that is labelled for use for major orthopaedic surgery. TXA has shown many benefits and only few adverse effects and we therefore found that the possible benefits to this patient group outweighed the possible harms.

10.4 Study II: Hip-Fracture Surgery on patients in Clopidogrel therapy is not associated with high risk of major blood loss. A retrospective observational study.

10.4.1 Study design
The study was a retrospective observational study conducted and reported in accordance with the STROBE-statement [47]. The study compared the SBL, TBL, number of RBC transfusions, incidences of massive transfusion, other bleeding related outcomes and 30 and 90 day mortality in a population of hip-fracture patients.

10.4.2 Target population
Our target population was all categories of hip-fracture patients who are receiving ADP Receptor Inhibitors (ADP-RI) at the time of admission and who are still under its effect during surgery.

10.4.3 Study population
Our study subjects were all patients treated for extra-capsular hip-fractures with an IMN who were receiving Clopidogrel at the time of admission and who underwent surgery <24 hours after discontinuation of Clopidogrel therapy. This study population was chosen as it has the greatest blood loss [11] and because the irreversible effect of Clopidogrel means that it can still be considered to be in full effect <24 hours after discontinuation [31,48]. This made it a suitable study population as we wanted to make inferences on the risks of very large and possibly uncontrollable blood loss in a population under the effect of ADP-RI. The study population does not match the target population exactly, but we feel confident that inferences from this study can be applied to all hip-fracture patients in ADP-RI therapy. The population we investigated represent the true clinical population, and the problems with lack of adherence to treatment and non-responders to therapy [49–51] would also hold true in other clinical settings.

10.4.4 Material
All patients had been treated according to department standards which included the discontinuation of Clopidogrel on admission.
Intervention: Patients in Clopidogrel therapy who underwent surgery for an extra-capsular hip-fracture <24 hours after admission and discontinuation of Clopidogrel therapy.
Control: Patients who were not in any form of Anticoagulation therapy (except ASA) and who underwent surgery for an extra-capsular hip-fracture <24 hours after admission.

10.4.5 Ethical considerations
This study was purely observational and did not involve any changes in treatment.

10.5 Study III: The case for continuing Clopidogrel® therapy during hip-fracture surgery. Results of a systematic review.

10.5.1 Study design
This study was a systematic review of the literature with meta-analysis of relevant results, conducted and reported in accordance with the PRISMA guidelines[52]. We searched the English language literature for any papers that reported on patients who underwent hip-fracture surgery while under the therapeutic effect of Clopidogrel.

10.5.2 Target population
Our target population was all categories of hip-fracture patients who are receiving ADP Receptor Inhibitors (ADP-RI) at the time of admission and who are still under its effect during surgery.

10.5.3 Study population
Our study population was a mix of hip-fracture types who underwent surgery while they were still under the therapeutic effect of Clopidogrel. The study population was drawn from six different papers on the subject, including **Study II** from this thesis.
The study population does not match the target population exactly, but we feel confident that inferences from this study can be applied to all hip-fracture patients in ADP-RI therapy.

10.5.4 Material
We searched PUBMED; EMBASE; Cochrane library and GreyOne for literature on the subject. We identified five studies in the search and included our own study on the subject. The search and data extraction was conducted independently by two of the authors.

10.5.5 Ethical considerations
The study was a literature review with no new interventions.

10.6 Study IV: Low incidence of pre-operative coagulopathies measured by Thrombelastography® (TEG®) in hip-fracture patients. A prospective observational study.

10.6.1 Study design
This study was a prospective blinded observational study conducted and reported in accordance with the STROBE-statement [47]. We prospectively conducted a blinded TEG-analysis on admission on 179 consecutive hip-fracture patients (all types).

10.6.2 Target population
The target population was patients with all types of hip-fractures and who were or were not in any form of anticoagulation medicine.

10.6.3 Study population
The study population was consecutive patients with hip-fractures admitted to our institution in the study period. The only exclusion criteria were related to missing data or follow-up. Our study population matches the target population which gives this study a high external validity.

10.6.4 Material
During the study period all patients admitted for a hip-fracture were subjected to a blinded TEG analysis. Results of these were analysed for outliers from the reference range and a prediction model based on the TEG variables to predict TBL was constructed.

10.6.5 Ethical considerations
The study only involved the drawing of an extra 5 ml of blood. No extra sampling beyond the standard regime was necessary. No interventions were undertaken based on results of the TEG analysis.

11 Methodological Considerations

11.1 Bias
Bias is the presence of a systematic error as opposed to a random error. Random errors are addressed by statistical hypothesis testing. The occurrence of random errors diminishes as sample size increases. Systematic errors are independent of the size of the study population. This means that statistical significance does not reflect the presence or absence of bias.
Many forms of bias have been described, but all bias can to some extent be classified in one of three categories:

- Selection bias
- Confounding bias (or “the mixing of effects”)
- Information bias

Selection bias means the systematic tendency to direct subjects into one or the other treatment category or the disqualification of subjects from a study population (i.e. by exclusion criteria). Confounding bias means that the confounding factor is a risk factor for the outcome but not part of the causal pathway where the exposure affects the outcome. Information bias occurs when endpoints are measured differently, in clinical trials this can often happen when a part of the treatment or appraisal of an outcome is left to the discretion of the clinician. Bias can be addressed and minimized through study design[53,54].

11.2 Study designs
In this thesis we have used four different types of study design.

11.2.1 Study I: Randomized Clinical Trial (RCT)
The RCT design addresses both selection bias and confounding bias by the nature of the design. When the study design includes blinding, information bias is also addressed.
The study was at risk of selection bias, specifically *healthy subject bias*. This was due to our exclusion criteria and the fact that it proved harder to gain informed consent from patients with dementia. This means that the study population does not exactly match the target population.
There was also a risk of information bias by *bias in detection of cases* as the cases of TE were only registered if it occurred in-hospital or when patients were re-admitted under this diagnosis. This could mean that we are underreporting the incidence of TE in both groups.
As to the question of *attrition bias* which is addressed through *intention to treat analysis,* we had three patients that “dropped out” after randomization. These were not systematic cases but rather due to errors of the investigators and chance. We therefore did no *intention to treat analysis.*

Another risk of information bias was by *bias of classification* as the patients total blood volume was calculated based on patient weight and height which was assessed by the admitting doctor.

11.2.2 Study II: Retrospective observational study

The retrospective design of this study conducted in a pre-specified time period of two years allowed us to investigate a large patient population without subject selection bias. Patients were only excluded based on lack of available data and we have no reason to believe that the lack of data represents a systematic error.
The retrospective design puts the study at risk of several types of information bias.
The study is at risk of *bias in detection of cases* as it is possible, though not likely, that patients that were in Clopidogrel treatment could be admitted without the admitting doctor recorded this therapy. This would lead to *contamination of controls,* but due to the fairly large control group this would probably not impact results.
Another important type of bias that is very plausible in this study is *bias by assessment* where patients receive special attention due to their special situation. This is very true for patients in Clopidogrel therapy who are about to undergo surgery.
Regarding the secondary outcomes of haematoma or wound discharge the study is at risk of *definition bias* as these complications are surgeon reported and subject to individual interpretation.

11.2.3 Study III: Systematic review with meta-analysis

The systematic review provides researchers with a chance to review the existing literature on a more or less narrowly defined subject. A review and meta-analysis of several high quality RCT´s is considered the highest level of evidence. A review of retrospective and prospective observational studies does not soar to these heights but still gives clinicians a resume of the evidence that exists on a given topic.
This study included five retrospective studies and one prospective study. All of these studies were at risk of the same types of bias as mentioned in **Study II** above.
The review itself is at risk of selection bias as only studies reported in English language were included in the analysis. This could mean that we are underreporting papers that have different conclusions.

11.2.4 Study IV: Descriptive blinded prospective observational study

The prospective and descriptive design of this study was chosen as the subject we examined had never been investigated before. The study design is inherently subject to selection bias, but we sought to counter this by including 200 consecutive patients admitted to our institution, without any exclusion criteria. The only exclusion criteria were related to missing data. There were no signs of a systematic pattern in the missing data.
To address information bias and the study was conducted in a blinded manner were clinicians were blinded to the results of the coagulation analysis.
The study is subject to bias by a host of confounders. We sought to find a relation between an on-admission coagulation analysis and TBL. The problem with this is that the outcome is a compound outcome. This is addressed through a multivariate analysis, but the multivariate analysis can only take the known/recorded confounders into account.

12 Summary of Results

12.1 Study I

A total of 72 hip-fracture patients treated with an IMN were analysed with 39 patients assigned to the placebo group and 33 patients to the TXA group.
We found a significant (p=0.029) decrease in TBL of 570.8 ml (95%CI = 61.7 — 1079.9) in the patients who were treated with the TXA regime. There were no incidences of TE in the TXA group and two incidences in the placebo group at 90 days follow-up.

12.2 Study II

We retrospectively identified 356 hip-fracture patients treated with an IMN who were eligible for inclusion during the study period (1st of January 2011 to 31st of December 2013). There were 36 patients in this group who received Clopidogrel or Dual Antiplatelet Therapy (DAPT) at the time of admission. All (n=356) patients underwent surgery <24 hours (mean: 14.1 hours; SD = 6.1) after admission. There was a non-significant (p=0.399) difference in means of -21 ml (95%CI: -73 — 29) of SBL in the Clopidogrel group. There were two cases of massive transfusion (>10 RBC transfusions in the first 24 hours after operation) reported in the control group and none in the Clopidogrel group. There were two cases of haematoma after surgery both of these were in the control group.
Additionally there were no cases of SBL >500 ml in the Clopidogrel group.

12.3 Study III

We identified six (including **Study II** in this thesis) English language studies that met our search criteria. These studies reported on 200 patients operated for hip-fractures while under the effect of Clopidogrel. We found no incidences of uncontrollable blood loss during surgery. There was a significantly increased OR of 3.64 (95%CI = 1.04 — 12.78, p = 0.044) for haematoma or wound discharge (labelled Surgical Bleeding Event (SBE)) post-operatively in the Clopidogrel group, but only one case of SBE lead to re-operation.
There was no difference in 30-day mortality with an OR of 0.99 (95%CI = 0.39 — 2.53, p = 0.986).

12.4 Study IV

A total of 179 patients were eligible for analysis. The TEG variables (R, MA, Angle and LY30) showed normal distribution in the population. A total of 25 patients (13.9%) had values outside the reference range normally used at our institution. We were not able to find any significant correlation between TEG values on admission and TBL.

13 Discussion and Conclusion

The aim of this thesis was to investigate the effect of different measures to reduce the blood loss in hip-fracture patients and to evaluate the effect of antiplatelet medicine on blood loss in these patients.

Through the four papers in this thesis we have investigated I) the effect of TXA on blood loss in hip-fracture patients; II and III) the incidence of large or uncontrollable blood loss in relation to hip-fracture surgery in patients who are taking Clopidogrel on admission; IV) the

incidence of coagulopathies as measured by TEG and the relation between TEG values and blood loss.

13.1 Tranexamic acid

TXA has been shown to have a blood sparing effect in several studies conducted on patients undergoing total joint replacement surgery and in spine surgery [55–58]. A single study conducted on mixed types of hip-fractures showed a non-significant difference favouring TXA [59]. Concerns on the safety of TXA have largely been put to rest by several large cohort studies. None of these studies found an association between TE or mortality and TXA [55,60–64].

Considering the present literature and our own results we would recommend TXA for all types of hip-fracture patients.

13.2 Clopidogrel and hip-fracture surgery

The intuitive notion of orthopaedic surgeons and anaesthesiologists is that surgery on patients who are in Clopidogrel therapy is associated with a risk of irreversible and uncontrollable blood loss during surgery [65]. This has led to the practice in many institutions of discontinuing therapy and waiting three or more days before performing surgery when patients are admitted for urgent surgery. In the case of hip-fracture surgery this is at odds with current evidence which states that hip-fractures should optimally be operated within 36 hours [66–70]. It is also at odds with the evidence regarding the risks associated with discontinuation of Clopidogrel therapy [71–74].

Our own results from **Study II** and **III** show that hip-fracture surgery on patients under the effect of Clopidogrel therapy is not associated with the hypothetical high risk of uncontrollable blood loss during surgery. We cannot, based on our material, conclude that the risk does not exist. But we can conclude that the risk is at least relatively small. This compared to the real risks of thromboembolic complications following discontinuation of therapy leads us to conclude that patients admitted for hip-fracture surgery who are in Clopidogrel therapy should be operated without discontinuation of therapy and without delay.

13.3 Thrombelastography (TEG) and hip-fractures

TEG (and ROTEM) have shown success in assessing coagulopathies in trauma patients [20,26] and have been used to guide transfusion therapy and reduce transfusion requirements in cardiac surgery, vascular surgery, liver transplantation and trauma surgery when it was compared to conventional coagulation tests [22,23,75–77].

We did not find a high prevalence of coagulopathies in hip-fracture patients, and the on-admission test could not predict blood loss in these patients.

We can therefore not recommend TEG as a routine on-admission coagulation test for hip-fracture patients. We cannot make inferences on its use in the per- or post-operative period where it may very well have a use in guiding therapy and identifying coagulopathies that have arisen in relation to surgery.

14 Perspective and Future Research

14.1 Tranexamic acid

Our results lead to new questions which should be further investigated.

Given the results TXA should be introduced as a standard treatment for all hip-fracture patients who do not have contraindications to its use. This includes patients with s-creatinine >120µmol/l, as long as the manufacturers guidelines are adhered to.
TXA should ideally be introduced in a protocolled manner in a prospective study with focus on safety outcomes such as TE and mortality.
Other study foci should be on the timing of the administration. We hypothesize that a dose of 1 gram given on-admission, in addition to the per-operative regime used in our study, would reduce the blood loss further as it would have an effect on the immediate blood loss associated with the fracture.

14.2 Clopidogrel

The results of our trial and review should lead to a change in standard treatment of hip-fracture patients in Clopidogrel therapy. This should be done protocolled and with long term follow-up of all patients with focus on TE and mortality. A pragmatic database could be set up where reports on number of patients in Clopidogrel therapy operated in each centre in Denmark could be collected together with reports of any incidences of uncontrollable blood loss during surgery. This database could be updated once a year during the annual orthopaedic DOS conference in Denmark. The database could potentially include all types of large orthopaedic operations.

14.3 Thrombelastography

On-admission TEG cannot be recommended based on our findings. But the method could still hold some promise in identifying patients who develop coagulopathies in relation to the surgical procedure. We hypothesize that some patients develop coagulopathies in relation to the surgical procedure, which constitutes a sort of “second hit” on the patients system. This could be investigated by performing TEG analysis on hip-fracture patients before and after surgery.
TEG may very well have a use in at-risk patients such as; patients in VKA treatment where TEG may be superior to traditional International Normalized Ratio measurements, and patients with inherent or acquired coagulopathies.

15 Literature

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16 Studies I-IV

16.1 Study I

Tranexamic Acid (TXA) reduces blood loss in patients with extra-capsular hip fractures; results of a randomized controlled trial.

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Abstract
Background: TXA has been shown to be a safe and reliable drug that can reduce blood loss in many types of surgery, including orthopedic surgery such as spine surgery and total joint replacements. Hip fracture patients sustain large Total Blood Loss (TBL) and consequently receive many blood transfusions. The danger of blood loss and transfusions prompts us to search for ways to reduce blood loss in this frail patient group. We hypothesized that TXA would reduce TBL in extra-capsular hip fractures. We chose extra-capsular hip fractures as our study group because these types of fracture suffer the largest blood loss.
Methods: A single-center placebo-controlled double-blinded randomized clinical trial was performed to test the hypothesis. Patients undergoing surgery for extra-capsular hip fractures were randomly allocated to two different groups. The TXA group was given a bolus of 1 gram of TXA preoperatively and 3 grams of TXA in 1 liter of saline as a 24 hour infusion postoperatively. The Placebo group was given a bolus of saline preoperatively and 1 liter of saline as a 24 hour infusion postoperatively. The primary outcome was the TBL, calculated based on hemoglobin measurements on admission and three days postoperatively. Secondary outcomes included number of transfusions, thromboembolic events (TE´s) and 30 and 90 day mortality.
Results: 72 patients were included in the final analysis with a significant mean reduction of 570.8 ml (p=0.029) in TBL from 2100.4 ml (SD = 1152.6) ml in the placebo group to

1529.6 ml (SD = 1012.7) in the TXA group. Also there was a non-significant mean reduction of 0.67 (p=0.187) in number of transfusions, favoring TXA. There were two TE´s in the placebo group at 90 day follow-up.
Conclusions: TXA significantly reduced TBL in extra-capsular hip fractures.
Level of Evidence: I

16.1.1 Introduction

Patients that sustain a hip fracture can suffer a TBL, in excess of 1.5 liters. The largest blood loss is seen among patients with extra-capsular fractures[1–3]. The number of transfusions depends on the local policy and the thresholds for transfusion vary [4]. Postoperative Anemia Necessitating Transfusions (PANT) are associated with increased morbidity in the form of increased time to ambulation, length of stay, infection rates, incidence of venous thromboembolisms (VTEs) and the risk of allergic reactions [4–9]. Tranexamic acid (TXA) has proven effective in reducing the need for transfusions by reducing the blood loss in both Total Hip and Total Knee Arthroplasty (THA and TKA) and in spine surgery[10–13]. In a study of 110 hip fracture patients, Zufferey et al suggested that TXA reduced the relative risk of receiving a blood transfusion[14]. A recent Cochrane review of 5 studies, of which 4 were conducted on hip or femoral fracture patients, concluded that TXA reduced the amount of blood transfusions[15]. Safety concerns regarding the risk of Thromboembolic Events (TE) and administration of TXA have largely been put to rest. TXA has been tested in several large cohorts. None of these studies found an increased risk of TE or mortality, not even among patients with one of seven TE risk factors or among cardiac patients treated with platelet aggregation inhibitors[10,16–20].
Our hypothesis was that the administration of TXA to patients with extra-capsular hip fractures would lead to a decreased TBL. Zufferey´s study[14] was conducted on a mix of hip fracture types, and showed a non-significant decrease in numbers of transfusions in the TXA group. We chose a single fracture type with a large average blood loss for our study and TBL as our primary outcome and performed the study within a standardized perioperative setup with fixed practices for hemoglobin measurements and standardized transfusion thresholds [21]. We did this to limit the potential bias of the indication for transfusion, which can vary from surgeon to surgeon, despite standardized transfusion thresholds.
We investigated if TBL in extra-capsular hip fractures was reduced by the administration of 1 gram of TXA preoperatively and a 24 hour infusion of 3 grams of TXA postoperatively. This regime was chosen on the basis of a suspected substantial postoperative blood loss in this surgical procedure [22,23]

16.1.2 Materials and methods

This single center, placebo controlled, double-blinded randomized clinical trial was performed in accordance with the provisions of the Declaration of Helsinki as revised in 2013. The protocol was drafted and the study conducted and reported in accordance with the CONSORT statement[24] and was approved by the regional ethics committee (Protocol number H-3-2011-004). Written informed consent was obtained from all patients before inclusion and randomization. Patient confidentiality was secured by the anonymization of all data which was kept in a secure server[25]. The study was registered at www.clinicaltrials.gov (cliniclatrials.gov ID NCT01535781).
No changes were made to the trial design during the study.

Consecutive patients undergoing hip fracture surgery for an extra-capsular fracture (AO type 31-A2.2 to 31-A3 [21]) with the insertion of a short Intramedullary Nail (IMN) were screened for inclusion. Exclusion criteria were; allergy to tranexamic acid, ongoing thromboembolic event (Deep Venous Thrombosis (DVT), Pulmonary Embolism (PE), arterial thrombosis or cerebral thrombosis), reduced kidney function (defined as a s-creatinine > 120 mmol/l), anticoagulation therapy including vitamin K-antagonists, direct thrombin inhibitors, direct factor X-a inhibitors and platelet aggregation inhibitors (not including acetylsalicylic acid), Disseminated Intravascular Coagulation (DIC), bleeding in the upper urinary tract (risk of obstruction), patients with a history of cramps, subarachnoid bleeding, malignancy, pathological fracture, previous operation in affected hip, more than one current fracture or bodyweight in excess of 100 kg.

Patients admitted to our institution, were assessed for eligibility on the morning of the operation. For logistical reasons it was not possible to assess patients operated immediately after admission in the evening or patients operated on weekends. Data was collected on admission, in the operating theatre, in the postoperative observation and in the orthopedic ward.

Included patients were given 1 gram of TXA (tranexamic acid, Pfizer, CT-USA) or placebo as an intravenous bolus during draping, just prior to surgery. This was followed by a postoperative 24 hour infusion of 3 grams of TXA or placebo mixed into 1 liter of isotonic saline.
Treatment of all included patients was conducted in accordance with department standards. Weight and height were assessed by the admitting doctor. Hemoglobin concentration was measured at the time of admission and immediately prior to surgery. Postoperatively it was measured on a daily basis until the third postoperative day giving a total of four hemoglobin measurements (day 1 to 4). Venous thromboprophylaxis was given every day at 10 p.m. as 5000 IE of Low Molecular Weight Heparin (Fragmin, Pfizer, CT-USA). All patients had a fascia iliaca compartment blockade on admission followed by epidural analgesia. They were operated under epidural anesthesia, according to department standard procedure with the insertion of a short IMN (IMHS-CP, Smith & Nephew, Memphis TN-USA). During surgery, blood loss was replaced by 6% hydroxyethyl starch 130/0.4 (Voluven, Fresenius Kabi, Germany) in a 1:1 ratio until hemoglobin concentration fell below the department transfusion threshold.

Transfusion threshold for patients followed department standards at 6.0 mmol/L (10 g/dL) both pre and postoperatively. Patients were examined for clinical signs of a TE on a daily basis, until discharge. After discharge patients were followed up minimum once at the outpatient clinic four months after surgery. Clinical signs of TE included calf tenderness, shortness of breath, chest pain or sudden onset of neurological deficits. In the event of clinical signs of TE, the relevant tests to confirm the diagnosis, according to international standards were performed. We did not do any routine ultrasound examination for DVT on patients. Information on TE from discharge to 90 days postoperatively was crosschecked with data from the national patient registry (that registers all diagnoses made on citizens admitted in any national hospital). Mortality was recorded during hospitalization and from the “national central person registry” where information on mortality is recorded on all national citizens. Information on number of transfusions was assessed directly from the hospital blood bank database. Surgical blood loss was assessed in the operating room

and recorded by the surgeon. All other data were prospectively recorded by the hospital staff in the patient record and assessed retrospectively by the primary investigator.

16.1.2.1 Outcomes

The primary outcome was the TBL which was calculated by the hemoglobin dilution method [26]. Nadler´s formula for blood volume[27] is used for calculating patient blood volume. For calculation of the TBL we used number of transfusions (55 grams of hemoglobin per transfusion (Hgb_{trans})), and the hemoglobin concentration on admission (Hgb_{adm}) and the hemoglobin concentration on the 3rd postoperative day, or the last available measure of hemoglobin concentration if this was not available (Hgb_{fin}) [3].

$$Womens\ Blood\ volume\ \ l\ \ = height\ (m)^3\ \times 0.356 + weight\ \ \ kg\ \ \times 0.033 + 0.183$$
$$Mens\ Blood\ volume\ \ l\ \ = height\ (m)^3\ \times 0.356 + weight\ \ \ kg\ \ \times 0.032 + 0.604$$

$$Hgb_{loss}\ \ g\ \ = Blood\ volume\ (l)\ \times\ \ Hgb_{adm}(g/L) - Hgb_{fin}(g/L)\ \ + Hgb_{trans}(g)$$

$$\boldsymbol{Blood\ loss\ \ \ ml\ \ = (Hgb_{loss}(g)/Hgb_{adm}(g/L) \times 1000}$$

The secondary outcomes were number of transfusions, risk reduction for receiving at least one transfusion and surgical blood loss during the operative procedure. The main safety outcomes were 30 and 90 day mortality and 90 day incidence of any TE´s during admission, re-admission or as registered in the “National patient registry”. No changes were made to outcomes in the course of the study.

16.1.2.2 Sample size

Based on a single previous study [3] on TBL in hip fractures and assuming a difference of at least 500 ml of TBL to be of clinical significance, two treatment groups of 60 persons each, 120 patients in total, were assumed to provide the study with a power of at least 80% at a two-sided type I error of 5%.

16.1.2.3 Interim analysis

An interim analysis was planned when reaching 60 inclusions. The interim analysis was conducted only on the primary outcome (TBL). At the time of interim analyses a total of 58 patients were eligible for analysis (32 in the placebo group and 26 in the TXA group). A two-sided t-test was performed at a significance level of 0.001 in order to detect extreme difference between TXA and placebo group. A difference in TBL of no less than 500 ml was considered a reason to halt the study. The 0.001 level was chosen as a simple approach to this interim analysis from the Haybittle-Peto boundary. This simple solution

was chosen because only one interim analysis was planned for the trial [28]. The significance level for the final analysis was chosen to be less than 0.05.

The randomization sequence was generated prior to study start, by a third party, who kept the sequence and its seed in a secure location for the duration of the study. The sequence was generated at www.randomization.com and packed into single, sequentially numbered, sealed envelopes by said third party. Two blocks with 60 envelopes each were created. Each block consisted of a random sequence of 30 intervention and 30 placebo allocations. Patients were enrolled in the study either by one of the study investigators or by a research assistant within the department. Patients enrolled in the study were assigned the next consecutive study number and the corresponding sealed envelope was put in their patient record. Prior to operation the sealed envelope was opened and the intravenous solutions were prepared according to the allocated group by staff members not otherwise involved in the treatment or study. Masking was ensured by the use of identical saline syringes for the bolus injection and identical drips for the 24-hour infusion. Patients, patient caregivers, data collectors and researchers remained unaware of the treatment given to the patients for the duration of the study period, including the author (TK) who performed the interim analysis by unlocking the randomization sequence, without unlocking the intervention type in the two analyzed groups.

16.1.2.4 Statistical methods

Analyses were conducted according to a pre specified statistical analysis plan. The trial was designed to show whether TXA was superior to placebo in reducing the TBL. QQ-plots for the TBL and number of transfusions did not show enough deviation to reject normality assumption, therefore a two-sided t-test was used to test for difference in TBL and number of transfusion between the TXA and placebo group.
For the comparison between TXA and placebo on the 30 and 90 day mortality a fisher's exact test was used, because of low mortality. Absolute risk reduction and numbers needed to treat was estimated from logistic regression, the model only included an effect of the placebo and TXA grouping.
P-values of less than 0.05 were considered statistically significant for all analysis if not stated otherwise. Analysis was done using R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria)

16.1.3 Results

16.1.3.1 Recruitment

Eligible patients were recruited from September 2011 to April 2014. Follow-up period was 90 days after surgery where TE events and mortality was recorded from the "National patient registry" and the "National Central Persons Registry" (CPR) respectively. See table 1 for baseline data of the included patients.

16.1.3.2 Reason for stopped trial

In April 2014 the head of department, who was not part of the research group, decided to end the study before reaching 120 included patients as planned in the protocol. Difficulties with recruiting patients because of department logistics and strict exclusion criteria had caused the study to take much longer than originally expected. The trial blocked several other trials planned in the department and therefore the study was terminated. Interim

analysis conducted in October 2013 had not shown any statistically significant difference between the two groups, so this was not a case of stopping for harm or benefit. The randomization sequence was not unlocked to the research group prior to the early termination of the trial (except for author TK as described above).

16.1.3.3 Participant flow

See fig. 1 for CONSORT flow chart. Of 190 patients assessed for eligibility, 75 were included, of which 2 did not receive any study medication as study participation was overlooked by the anesthesia nurse and 1 had a cerebral thrombosis before study medication was received and had the surgery postponed two days. A total of 72 patients (51 females), with 33 patients in the TXA group and 39 in the placebo group, were included in the final analysis.

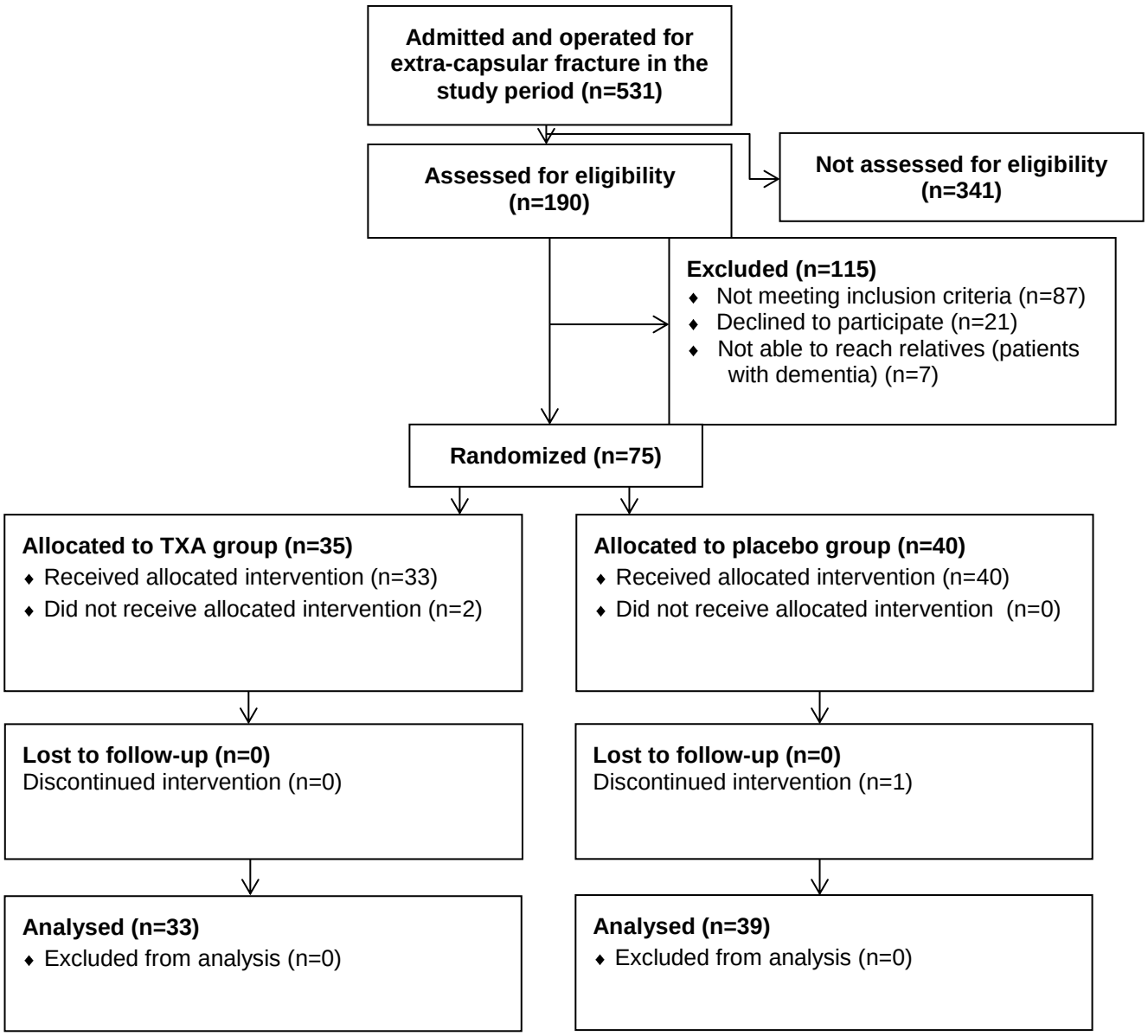

Fig.1. CONSORT flow chart.

16.1.3.4 Outcomes and estimation

Table 1 summarizes our main findings. TBL was calculated in both groups. Mean TBL was 2100.4 ml (SD = 1152.6) in the placebo group, and 1529.6 ml (SD = 1012.7) in the TXA group. Difference in means was 570.8 ml (95%CI = 61.7 — 1079.9; p=0.029) in favor of TXA treatment. (See fig. 2)

Mean number of transfusions were 3.1 (SD = 2.3) in the placebo group and 2.4 (SD=1.9) in the TXA group (95%CI= - 0.34 — 1.68; p=0.187). The Absolute Risk Reduction of receiving at least one transfusion was 0.058 (95%CI: - 0.079 — 0.320) favoring TXA.

Mean surgical blood loss was 236.0 ml (SD = 218.6) in the placebo group and 187.5 ml (SD = 130.1) in the TXA group (95%CI: -36.8 — 133.9; p= 0.260). The Number needed to treat for receiving at least one less unit of blood was 35.8 (p=0.751). (See fig. 3)

The hemoglobin on admission was 8.0 mmol/l (SD = 1.0) in the placebo group and 7.4 mmol/l (SD = 0.9) in the TXA group (p=0.024). (See figs. 4 and 5)

Three patients died during hospitalization giving an in-hospital mortality of 4.1%. Two of these patients were in the placebo group. 30-day mortality was 7% (n=5) (TXA group: 12% (n=4); Placebo group: 2.5% (n=1)) and 90 day mortality 18% (n=13) (TXA group: 27% (n=9); Placebo group: 10% (n=4) (p=0.07)), cumulated. There were two incidents of TE within the 90 day postoperative period. One patient had a cerebral infarction from a thrombosis 53 days postoperatively, and another patient had a DVT 21 days postoperatively. Both of these patients were in the placebo group. No unintended effects or direct harms were recorded that could be related to the intervention in this study.

Table 1

		Total	Placebo	TXA	mean dif	95%CI	p value
Sex	F	51 (70.8%)	25 (64.1%)	26 (78.7%)			0.269
	M	21 (29.1%)	14 (35.8%)	7 (21.2%)			
Age	mean	77.2 (SD: 12.2)	75.0 (SD: 12.6)	79.8 (SD: 11.5)	-4.8	-10.4 — 0.9	0.098
BMI	mean	22.8 (SD: 4.4)	23.0 (SD: 4.7)	22.6 (SD: 4.2)	0.4	-1.7 — 2.5	0.714
ASA-score	1	2 (2.7%)	1 (2.5%)	1 (3.0%)			0.299
	2	53 (73.6%)	26 (66.6%)	27 (81.8%)			
	3	17 (23.6%)	12 (30.7%)	5 (15.1%)			
Hgb on admission (mmol/l)	mean	7.7 (SD: 1.0)	8.0 (SD: 1.0)	7.5 (SD: 0.9)	0.5	0.1 — 2.5	0.024
Received a transfusion	No	12 (16.6%)	6 (15.3%)	6 (18.1%)			0.762
	Yes	60 (83.3%)	33 (84.6%)	27 (81.8%)			
TBL (ml)	mean	1838.8 (SD: 1120.4)	2100.4 (SD: 1152.6)	1529.6 (SD: 1012.7)	570.8	61.7 — 1079.9	0.029
Surgical Blood Loss (ml)	mean	213.5 (SD: 183.3)	236.0 (SD: 218.6)	187.5 (SD: 130.1)	48.6	-36.8 — 133.9	0.260
Transfusions (U)	mean	2.8 (SD: 2.19)	3.1 (SD: 2.3)	2.4 (SD: 1.9)	0.67	-0.34 — 1.68	0.187
30 day mortality		5 (6.9%)	1. (2.5%)	4 (12.1%)			
90 day mortality		13 (18.0%)	4 (10.2%)	9 (27.2%)			

Table 1. Numbers are given as absolutes with percentages or as mean (Standard Deviation).

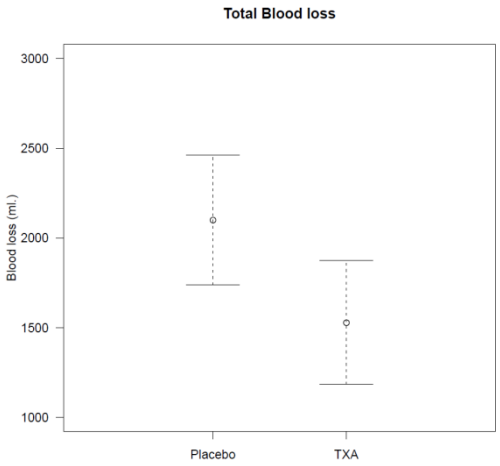

Fig. 2.

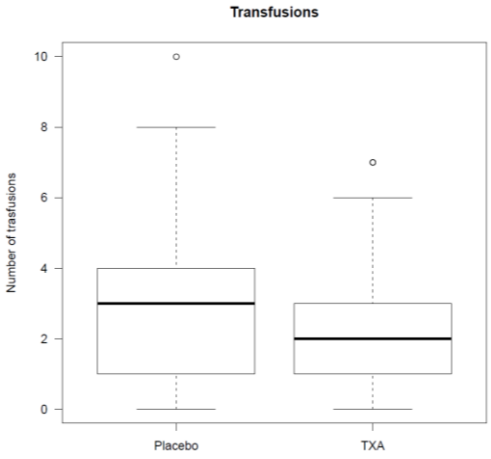

Fig. 3.

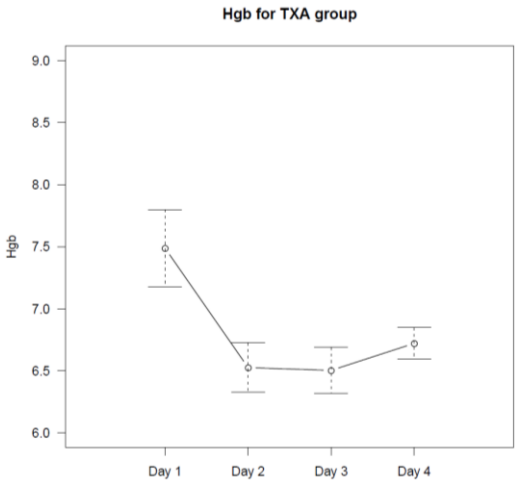

Fig. 4.

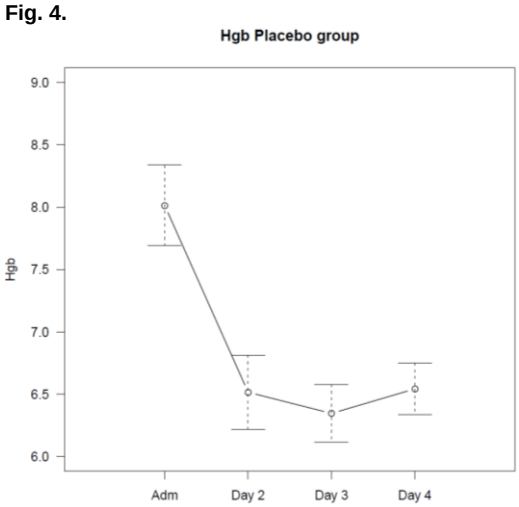

Fig. 5.

16.1.4 Discussion

The administration of a pre- and postoperative regime of TXA gave a significant decrease in the TBL of nearly 600 ml in patients with extra-capsular hip fractures operated with a short IM-nail. Also a statistically non-significant difference in number of transfusions of 0.6 in favor of TXA was observed. This difference was in spite of the statistically significant higher hemoglobin on admission in the placebo group.
A theoretical explanation for these results could be that TXA´s antifibrinolytic properties provide a stronger postoperative blood clot, thus preventing a substantial postoperative blood loss. Smith et al showed that a large proportion of the TBL occurs between the time of fracture and the time of operation[2]. We theorize that the initial blood clot formed at the time of fracture is broken up during surgery, thus causing a “second hit” that produces further blood loss. The application of TXA pre and postoperatively helps reduce this “secondary” blood loss.
Our findings support earlier studies showing a blood sparing effect by the application of TXA to hip fracture patients. In 110 patients with a mix of different hip fracture types and operation types, Zufferey et al showed a non-significant (p=0.057) relative risk reduction for receiving one blood transfusion of 30% (p=0.055, CI= -1 to 52%) by administering TXA pre and postoperatively[14].The TXA was given at a dose of 15 mg/kg, preoperatively and 3 hours postoperatively. Transfusion thresholds are comparable to those in our study.

This study was not designed to make inferences on mortality or incidence of TE, and no statistically significant difference was seen between the two groups at 30 and 90 days. Zufferey et al found a higher risk for TE in the TXA group, with DVT as the most frequently observed adverse event. These were only asymptomatic DVT´s detected by mandatory ultrasound examination, and the clinical significance of this finding is questionable. A Cochrane review of 2013 analyzed the findings of five studies investigating the effect of TXA administration. Two of the included studies (including Zufferey´s results) were on hip fracture surgery and two other studies were on femoral fractures. The last study was on emergency cardiac surgery patients. All of the studies tested the per-operative administration of TXA against placebo in a randomized controlled setup. Only three of these studies reported the incidence of TE. The Cochrane review found that TXA reduces the amount of transfusions in emergency or urgent surgery, but could not conclude on other clinically relevant outcomes such as TE[15]. We did not identify any other studies on the subject of hip fractures and TXA. Several large scale studies have concluded that the use of TXA is not associated with an increased incidence of TE even in patients with increased risk of TE and patients in ongoing platelet aggregation inhibitor treatment[10,17–20].

There are several limitations to our study:
The study was stopped before the planned number of patients was reached. The decision to cut the study short was not a consequence of stopping for benefit or harm, and the decision was out of the hands of the research group.
The primary outcome is a calculation based on several clinical measurements that could be a source of error. The hemoglobin measurements can be affected by the initial dehydration and the rehydration following admission. This should however not affect the difference between the groups.

The report of TE in our group is limited to the patients who were re-admitted with a TE. We were not able to retrieve the cause of death for patients who died within the 90 day follow-up period. This could mean that we are underreporting the incidence of TE in the TXA group, as we are overlooking the immediately fatal TE´s.
A large proportion of the patients assessed for eligibility had to be excluded due to our exclusion criteria. The main reasons for excluding patients were an s-creatinine >120 µmol/L or the use of antithrombotic drugs. Seven patients with dementia were found eligible but could not be included because it was not possible to reach their relatives in time. This may have led to selection bias where only the fittest patients are included.
The study has several strengths compared with previous studies:
Only one type of fracture and operation was investigated, which eliminated one possible source of bias due to greater homogeneity in blood loss profiles.
A clinical standardized set-up with the departments specialized multimodal hip-fracture protocol [21].

The implications of this study combined with the findings of previous studies and the reported safety of TXA from other large-scale studies suggests that TXA administered pre and postoperatively for hip fracture patients can be recommended. Our exclusion criteria included s-creatinine >120 µmol/L, but it is important to remark that the drug is labeled as safe up and until 500 µmol/L where a reduced dose is used. We cannot draw conclusions regarding patients in antithrombotic treatment but a recent study with over 1000 cardiac surgery patients showed a protective effect of TXA on blood loss in patients receiving PAI´s without cessation of treatment prior to surgery and no increase in mortality or morbidity, including TE´s. This study even suggests that TXA would allow for surgery without cessation of PAI´s[20]. These suggestions cannot be directly transferred to the hip fracture patient, but they are interesting in the perspective of new studies in this field.

In conclusion, it appears that the use of TXA can be recommended in patients undergoing hip fracture surgery to reduce the TBL. But it is important for us to stress that the implementation of TXA use in this frail patient group should be done in a protocolled manner with focus on adverse events such as TE.

Future studies should not focus on comparing TXA to placebo, but rather focus on the proper timing of the doses.
We theorize that because the largest blood loss takes place at the time of the fracture, further reductions in blood loss could be achieved by administering a dose of TXA for hip fracture patients, on admission. Studies could be conducted as larger cohort studies with long term follow-up, which would allow for some of the excluded sub-groups from our study to be analyzed, including patients with impaired kidney function, who could be given reduced doses as per the manufacturer's recommendations. Such larger study cohorts with long follow up periods would also allow for more definitive conclusions on the safety of TXA in regard to TE´s and mortality in hip-fracture patients.

16.1.5 Source of funding

This study was funded by the department of orthopedic surgery and the department of anesthesiology at our institution. All medications used in the study were funded by the departments. No external funding was received to conduct this study.

16.1.6 Literature

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16.2 Study II

Hip-Fracture Surgery on patients in Clopidogrel therapy is not associated with high risk of adverse bleeding events

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Abstract
*Background:*Patients in Clopidogrel therapy alone or in combination with acetylsalicylic acid (Dual Antiplatelet Therapy (DAPT)) presenting with a hip-fracture represent the surgeon with a dilemma. Should treatment be continued, with the risk a major blood loss during and after surgery? Or should treatment be discontinued and surgery delayed, with the risk of increased morbidity and mortality due to delay of surgery and a thromboembolic event after surgery due to discontinued antiplatelet therapy? We hypothesize that the risk of a major blood loss in patients that are still under the effect of Clopidogrel or DAPT during or after hip-fracture surgery is relatively low.

Methods: We conducted a retrospective case-control study on patients undergoing surgery with a short intramedullary nail for extra-capsular hip-fractures at our institution, in the period from the 1st of January 2011 to the 31st of December 2013. Primary outcome was Surgical Blood Loss (SBL). Secondary outcomes were Total Blood Loss (TBL), Red Blood Cell (RBC) transfusions and incidents of massive transfusion.

*Results:*We identified 36 patients receiving Clopidogrel or DAPT on admission. 320 patients were included in the control group. Mean SBL in the control vs. Clopidogrel group was 235.4 [SD: 238.1] ml vs. 213.6 [SD: 131.7] ml. TBL was 2006.3 [SD: 1072.6] ml vs. 2249.1 [SD: 1010.2] ml and number of RBC transfusions were 3.0 [SD: 2.3] U vs. 3.4 [SD: 2.2] U, with no significant difference between groups.
There were no incidences of massive transfusion (>10 U in <24 hours) in the Clopidogrel group. Maximal SBL was 500 ml in the Clopidogrel group.

*Interpretation:*Our study results adds to the growing evidence that hip-fracture surgery on patients under the effect of Clopidogrel or DAPT is not associated with a high risk of major blood loss or massive transfusion. We conclude that hip-fracture surgery on patients receiving Clopidogrel or DAPT should be conducted without delay and without withdrawal of therapy.

16.2.1 Introduction

16.2.1.1 Background

Patients in Clopidogrel therapy alone, or in combination with acetylsalicylic acid (Dual Antiplatelet Therapy (DAPT)) presenting with a hip-fracture represents a dilemma to the orthopedic surgeon. The intuitive notion is that the patients are at an increased risk of a large uncontrollable blood loss due to the irreversible antiplatelet effect of the therapy. This notion may be true in regards to cardiac surgery[1], but we have found no evidence to support this notion among hip-fracture patients. Current guidelines on the management of these patients are solely based on expert consensus panels[2].
Due to the irreversible platelet inhibition induced by Clopidogrel, baseline aggregation is not normalized before new platelets have been formed. This is not achieved before 3-5 days after withdrawal of the therapy. Surgeons that wish to reduce the theoretical risk of a large blood loss will therefore have to wait at least 3 days[3,4].This is at odds with the increased mortality and morbidity related to delay to surgery in these patients[5,6]. The withdrawal of therapy in patients with coronary stents has been shown to have a detrimental effect, with very high mortality rates[7,8]. Withdrawal also seems to be associated with an increased risk of acute coronary syndrome and death, in other patient categories[9].

Is the clinical practice of abrupt withdrawal of Clopidogrel therapy and delay to await the return of platelet function in hip-fracture patients a rational approach? If the risk of an uncontrolled bleeding is minimal and the risk of thromboembolic events is not, then this practice should probably be reconsidered.

16.2.1.2 Objective

We want to investigate if patients who are under the effect of Clopidogrel treatment at the time of surgery have significantly higher blood losses and are at higher risk of massive transfusion than patients who are not using Clopidogrel, when treated in a standardized perioperative pathway with standardized operative and transfusion practice.
Our primary endpoint was SBL. Secondary endpoints included Total Blood Loss (TBL) (calculated as described by Foss et al.[10]), number of RBC transfusions and the risk of an uncontrolled bleeding that leads to massive transfusion (defined here as >10 Red Blood Cell (RBC) transfusions within 24 hours[11]).

16.2.2 Patients and method

16.2.2.1 Study design/setting and participants

This study was designed, conducted and reported according to the STROBE statement[12]. The study was registered at ClinicalTrials.gov (ID: NCT02391883). We did a retrospective case control study to test our hypothesis. The population investigated here was also used for another study on mortality and blood loss (not yet published). We collected data on all patients who sustained an extra-capsular hip-fracture operated with a short intramedullary nail according to the surgical algorithm [13] at our institution from the 1st of January 2011 to the 31st of December 2013. Patients using Clopidogrel (Plavix®, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Bridgewater, NJ) alone or in combination with acetylsalicylic acid (DAPT) at the time of admission and operated within the first 24 hours from time of admission were included in the case group. Patients using Clopidogrel are routinely discontinued in their treatment on admission to our department, unless the indication for treatment is coronary stent insertion.
Exclusion criteria were, patients operated >24 hours after admission, patients in other forms of anticoagulation medication except acetylsalicylic acid (including vitamin K antagonists, dipyridamole, dabigatran, apixaban and rivaroxaban), missing data on blood loss in patient chart, missing blood samples in the first 4 days and extra-national patients (follow up not possible). Patients operated on both sides during the inclusion period were only included with data on their latest operation.
The remaining patients were included in the control group.

16.2.2.2 Variables and Data sources

Our primary outcome was SBL as measured directly through collection in suction drains and collection bags in the draping, weighing of tissues and estimated by the surgeon and operating room staff. Secondary outcomes were: TBL, number of RBC transfusions from admission to the 3rd day, 30 and 90 day mortality and incidents of uncontrollable bleeding that led to massive transfusion in the operating room or in the first 24 hours postoperatively. Massive transfusion was defined as >10 RBC transfusions given within 24 hours [11].
Patients were identified using the local operations database. Data was collected from clinical databases including; the operations database, the patient chart database, the clinical biochemistry database and the blood bank database on transfusions. All data was

stored in a secure local database created for this study. We obtained data on patient sex, age, weight, height, anticoagulation medication on admission, time from admission to operation, duration of surgery, American Society of Anesthesiologists' (ASA-score) classification of Physical Health, per-operative blood loss as observed by the surgeon and OR staff, Hemoglobin concentration on admission and the first 3 days, number of RBC transfusions, number of Fresh Frozen Plasma (FFP) transfusions, number of platelet transfusions, reports of postoperative wound discharge or hematoma in the patient charts and time of death.
All patients were operated and treated postoperatively according to department standards. Department transfusion threshold is a hemoglobin concentration <6.0 mmol/l (~10 g/dl). During surgery blood loss was replaced by 6% hydroxyethyl starch 130/0.4 (Voluven, Fresenius Kabi, Germany) in a 1:1 ratio until hemoglobin concentration fell below the transfusion trigger point. Venous thromboprophylaxis was given as 5000 IE of Low Molecular Weight Heparin (Fragmin, Pfizer, CT-USA) the evening before surgery.

16.2.2.3 Statistical analysis

We arranged the patients in two groups: A Clopidogrel group and a control group. Difference between the Clopidogrel and control group on SBL, TBL and number of RBC transfusions was tested using a two-sided t-test. Normality assumption was evaluated using QQ-plots.
We did not do a power calculation as our study period was limited by practical and logistical causes.
Statistical significance was defined as p values of less than 0.05. All analysis was done using R 3.0.2 (R foundation for Statistical Computing, Vienna, Austria)
We did not plan any subgroup analysis beyond the analyses described above.
Missing data on blood loss or transfusions was addressed by exclusion from the analysis.
We did not match the control group to the Clopidogrel group, but included all patients not receiving anticoagulation medication in the control group.

16.2.3 Results

We identified 446 patients treated with a short intramedullary nail for an extra-capsular hip-fracture at our institution during the study period. See fig 1. for patient inclusion flowchart. A total of 356 patients were included in the final analysis. Out of this group we identified 36 patients taking Clopidogrel. 24 of these were in DAPT. 12 patients were in Clopidogrel therapy alone. The indications for treatment were: CNS thrombosis (n=14); Unstable Angina (n=8); Peripheral Atherosclerosis (n=3); Myocardial Infarction (n=2); Insertion of stent >24 months earlier (n=1); and Unknown indication (n=8). All patients had their treatment discontinued on admission, to be resumed postoperatively.
All analyzed patients were operated within 24 hours of admission (n=356).
(See table 1 and 2 for descriptive data and main findings.)

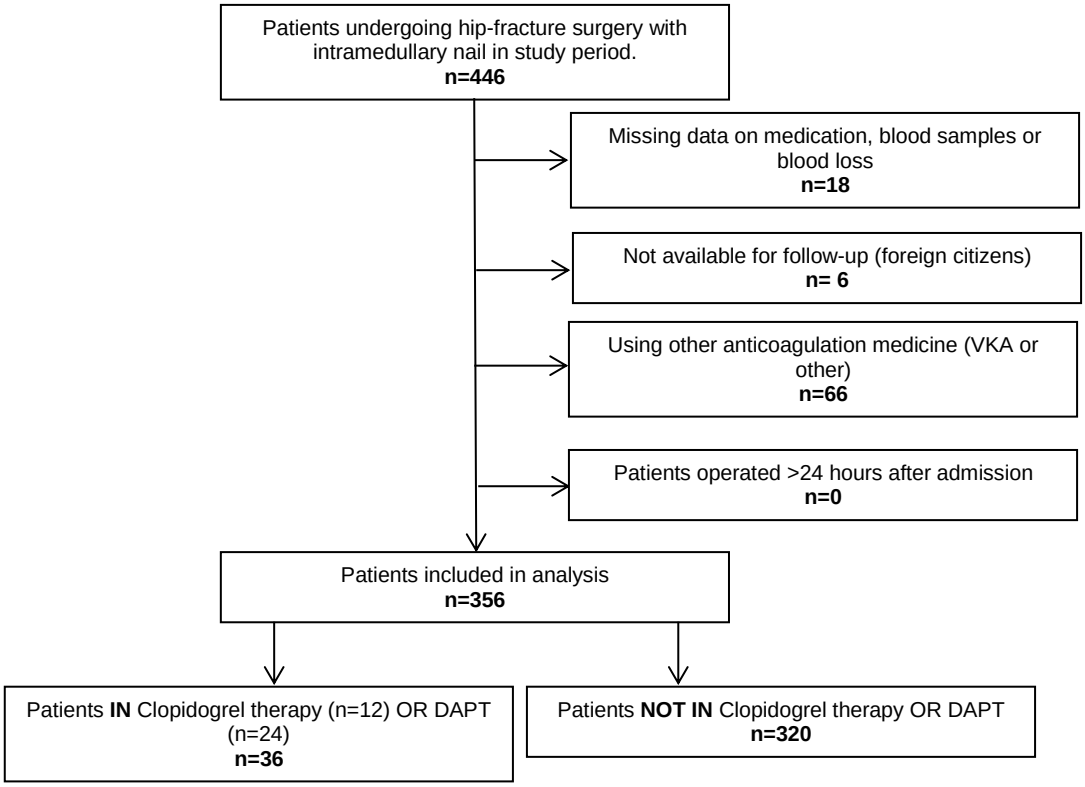

Fig. 1. Patient flow-chart.

Assuming normal distribution we tested difference of means with a t-test.
For the SBL there was a non-significant mean difference of -21 ml (95%CI: -73 — 29; p = 0.399) in the Clopidogrel group compared to the control group; TBL showed a non-significant mean difference of +243 ml (95%CI = -117 — 602; p = 0.181) in the Clopidogrel group compared to the control group, and number of transfusion had a mean difference of +0.4 transfusions (CI: -0.33 — 1.22; p = 0.251) in the Clopidogrel group compared to the control group.
Only two of the patients included in our analysis received massive transfusion in relation to the operation (>10 RBC transfusions in the first 24 hours of operation). Two other patients received >10 RBC transfusions during their admission, but not within a 24 hour period. All four patients were in the control group.
There were two cases of hematoma after surgery. Both were in the control group and none of them were re-operated as a consequence of the hematoma.
One patient in the Clopidogrel group received 2 FFP transfusions during surgery, and another patient in the Clopidogrel group received 2 platelet transfusions during surgery.
Maximal SBL was 500 ml in the Clopidogrel group vs. 2200 ml in the control group.
As an additional analysis we identified outliers in SBL and TBL and found six patients with SBL > 1000 ml in the control group and none in the Clopidogrel group. We identified eight patients with a TBL>5000 ml in the control group and none in the Clopidogrel group.

Table 1: Patient Characteristics and Primary Outcomes

		All (n=356)	Control Group (n=320)	Clopidogrel Group (n=36)
Age (yrs)	mean	79.0	78.7	81.1
	sd	11.7	11.9	9.2
Sex	F	240 (67.4%)	215 (67.1%)	25 (69.4%)
	M	116 (32.6%)	105 (32.9%)	11 (30.6%)
ASA-score	1&2	241 (67.7%)	226 (70.6%)	15 (41.7%)
	3&4	115 (32.3%)	94 (29.4%)	21 (58.3%)
Admission to operation (hours)	mean	14.1	14.2	13.2
	SD	6.1	6.1	5.9
Acetylsalicylic acid use	Yes	116 (32,6%)	92 (28.7%)	24 (66.6%)
	No	240 (67.4%)	228 (71.3%)	12 (33.4%)
Hgb on admission (mmol/l)	mean	7.6	7.6	7.4
	SD	1.0	1.0	1.0
SBL (ml)	mean	233.2	235.4	213.6
	SD	229.5	238.1	131.7
SBL >1000 ml		6 (1.6%)	6 (1.8%)	0
TBL (ml)	mean	2030.9	2006.3	2249.1
	SD	1067.6	1072.6	1010.2
TBL >5000 ml		8 (2.2%)	8 (2.5%)	0
RBC transfusions (U)	mean	3.0	3.0	3.4
	SD	2.3	2.3	2.2
Massive Transfusion (>10 U in 24 h)		2 (0.5%)	2 (0.6%)	0
30 day mortality		25 (7.0%)	23 (7.2%)	2 (5.5%)
90 day mortality		47 (13.2%)	43 (13.4%)	4 (11.1%)
1 year mortality		96 (26.9%)	83 (25.9%)	13 (36.1%)

Table 2: Difference between groups

Clopidogrel vs. Control	Mean Difference	95% CI Lower	95% CI upper	p-value
SBL (ml)	-21,8076	-73,0741	29,4588	0.39866
TBL (ml)	242,7645	-117,3453	602,8743	0.18123
RBC Transfusions (U)	0,4479	-0,3287	1,2245	0.25134
30 day mortality	-	-	-	0.985
90 day mortality	-	-	-	0.896

16.2.4 Discussion

We found no significant difference in SBL, TBL or number of RBC transfusions between the control group and the group using Clopidogrel on admission. There were no incidences of massive transfusion in the Clopidogrel group versus two incidences in the larger control group. The largest SBL in the Clopidogrel group was 500 ml.

Although not significant we saw a trend towards an increased TBL and number of RBC transfusions, but these differences hardly represent a clinically significant increase in blood loss.

Our study is limited by the small number of patients, and the retrospective design giving some confounders that are hard to address. The question of patient adherence to treatment[14,15] and the relatively high incidence of non-responders to Clopidogrel (reported between 6-24%)[16] can have a positive effect on results in the Clopidogrel group.
Still, the study has high external validity as it reflects the actual clinical situation on a consecutive group of hip-fracture patients with large blood losses, in which patients were under effect of Clopidogrel treatment at the time of operation.

Our study is unique in the literature as we only report on patients operated with a short intramedullary nail. A subtype of hip-fractures that have some of the largest blood losses reported among orthopedic patients[10]. Patients were treated in a standardized uniform set-up, both pre- and post-operatively, giving a very homogenous group of patients[13]. This eliminates some of the potential bias from many of the previously conducted studies that include a mix of operation types and therefore also a mixed profile of blood losses in their groups.

All patients were operated within 24 hours of admission. Given the irreversible effect on platelets elicited by Clopidogrel, baseline aggregation is not achieved before new platelets are formed, which takes at least 3-5 days [3,4]. The patients in Clopidogrel therapy or DAPT can therefore be assumed to be under full therapeutic effect during surgery.

Our results indicate that the risk of a large blood loss (surgical or otherwise) or massive transfusion in hip-fracture patients under the effect of Clopidogrel therapy or DAPT at the time of surgery is low. These findings confirms the findings of previous studies performed on hip-fracture patients receiving Clopidogrel or DAPT on admission [17–29]. All of these studies, except one[25], are retrospective. Most of them have less than 50 patients in the Clopidogrel group. They all conclude that there is no reason to delay surgery, and no reason to withdraw therapy. None of these studies report incidences of massive uncontrollable bleeding during or after surgery. Two studies on the subject have a more conservative conclusion, stating that it is safe to operate within five days and that an individualized approach based on patient risk factors should be considered [30,31]. One study concludes that there is no disadvantage to delay of surgery [32].

Our findings add to the growing evidence that surgery on patients receiving Clopidogrel or DAPT is not associated with a high risk of major blood loss or massive transfusion. None of the previous studies or the present study can rule out a theoretical risk of major uncontrollable bleeding during surgery in these patients. A larger study that is able to draw more definitive conclusions on the risks associated with this practice has not yet been conducted.
Given the evidence that is available on the very real risks associated with withdrawal of therapy and delay to surgery, we recommend hip-fracture surgery without delay and without withdrawal of Clopidogrel therapy or DAPT. But due to the persisting theoretical risk of massive bleeding, this should be done in a protocolled manner.

16.2.5 Funding

No external funding was received for this study.

16.2.6 Literature

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16.3 Study III

The case for continuing Clopidogrel® therapy during hip-fracture surgery. Results of a systematic review with meta-analysis.

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Abstract

Research question: Is hip-fracture surgery conducted on patients under the effect of Clopidogrel therapy safe?

Study design: Systematic review of the English language literature, with meta-analysis of Surgical Bleeding Events (SBE) and 30-day mortality.

Results: In six studies of 200 patients operated for hip-fractures while under the effect of Clopidogrel we found; no incidences of uncontrollable blood loss during surgery; a significantly increased OR of 3.64 (95%CI = 1.04 — 12.78, p = 0.044) for SBE in the Clopidogrel group; and no difference in 30-day mortality OR of 0.99 (95%CI = 0.39 — 2.53, p = 0.986).

Interpretation: Continued Clopidogrel therapy carry an increased risk of hematoma or wound discharge (SBE) after hip-fracture surgery, but does not carry a high risk of uncontrollable blood loss during surgery, nor does it impact 30 day mortality. We recommend that hip-fracture surgery should be carried out without delay and without discontinuation of Clopidogrel therapy before surgery.

16.3.1 Introduction

16.3.1.1 Background

Hip-fracture patients should optimally receive surgery as fast as possible and preferably within 36 hours [1–5], but the increasing use of the Platelet Aggregation Inhibitors (PAI) such as Clopidogrel (Plavix®, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Bridgewater, NJ), alone or in combination with aspirin (dual antiplatelet therapy (DAPT)) poses a dilemma for orthopaedic surgeons and anaesthesiologists [6].
Should the treatment be continued in order to reduce the risk of Thromboembolic Events (TE's)[7,8] or, be discontinued to avoid excessive and/or uncontrollable blood loss and then resumed after surgery [9].

The problem with the latter solution is two-fold: The active metabolite of Clopidogrel irreversibly inhibits ADP-induced platelet aggregation. Baseline platelet aggregation and bleeding times are not achieved before ~5 days after discontinuation of the drug, subject to individual variation, when new platelets have been formed [10]. So to reduce risk of bleeding surgeons will have to delay surgery at least 3 days from discontinuation[11], which increases risk of morbidity and mortality due to delay of surgery, as mentioned above.

Secondly the discontinuation of Clopidogrel puts the patient at an increased risk of TE´s postoperatively[7,8]. Patients with coronary stents are especially vulnerable in the period from insertion until full endothelialization of the stent, where discontinuation can have catastrophic consequences[12,13].
The existing guidelines on the discontinuation of Clopidogrel are based on expert consensus panels, however in the case of DAPT there is evidence to support that aspirin should never be discontinued [9,14,15]. The risk of death related to discontinuation of therapy depends on factors such as: the indication for Clopidogrel therapy; time since the event that set the indication for Clopidogrel therapy (Stent insertion, Coronary Artery Bypass Graft and others); and other inherent factors such as the patients ejection fraction and diabetes status [7]. Several studies report a significant increase in mortality related to discontinuation of therapy [12,13] and one study report an increased 30-day mortality in hip-fracture patients in PAI treatment related to delay in surgery [16]. There is no evidence of benefit to support the practice of "bridging" with different anti-thrombins [17].

So to put it simply; the surgeons dilemma is whether to put the patient at risk of death due to bleeding or to put the patient at risk of death due to delay of surgery and discontinuation of Clopidogrel therapy.
The risk of death due to delay of surgery and discontinuation of therapy has been well documented, as outlined above.
On the other hand the risk of death due to excessive blood loss in hip-fracture patients in PAI treatment remains debatable [9].
The typical notion of the orthopaedic surgeon and anaesthesiologist is that continued Clopidogrel therapy may lead to an uncontrolled and irreversible bleeding during surgery that leads to massive transfusion and potential death.

16.3.1.2 Objective

We hypothesize that the risk of surgical bleeding to a degree which has a consequence for the patients outcome or leads to immediate death, in patients that continue Clopidogrel or

DAPT therapy during hip-fracture surgery, is insignificant compared to the risk of death due to delay of surgery and/or death due to discontinuation of therapy.
We did a systematic review of the English language literature, to identify studies with patients undergoing surgery for hip-fractures that were not discontinued in Clopidogrel or DAPT therapy OR who were still under the effect of treatment at the time of surgery (defined as operation <24 hours after discontinuation of therapy).

16.3.2 Methods

16.3.2.1 Literature search

The study was designed, conducted and is reported according to the PRISMA-statement[18].This study was registered at the PROSPERO centre for reviews (reg. number: CRD42015016451). We used a *"Patient-Problem/Intervention/Comparison/Outcome"* (PICO) strategy to build our search strategy. Two authors (PT and AG) conducted the search, screening, data extraction and risk of bias assessment independently. In cases of disagreement a third author was involved in the process (AT). We searched PUBMED, EMBASE, The Cochrane Library, Grey Literature database (www.opengrey.eu) and Clinicaltrials.gov for relevant studies. We limited our search to English language. The last update of the search was done on the 9th of February 2015.

PUBMED:

(((Clopidogrel) AND "Hip-fractures"[Mesh])) OR (("Platelet Aggregation Inhibitors"[Mesh]) AND "Hip-fractures"[Mesh]).

EMBASE:

((platelet aggregation inhibitor AND hip-fracture) OR (Clopidogrel AND hip-fracture))

All types of studies involving patients in Clopidogrel/DAPT therapy undergoing hip-fracture surgery without discontinuation of therapy prior to surgery OR where surgery was performed <24 hours after discontinuation were considered relevant for inclusion. Studies without a relevant control group were not included.

16.3.2.2 Data extraction

The following data was extracted: operation type; control group type (matched or unmatched); number of subjects; age; ASA score; delay to surgery; number of Red Blood Cell (RBC) transfusions; transfusion threshold; Major Surgical Bleeding Events (MBSE)(defined as hematoma; continuous bleeding; or as otherwise stated in the manuscripts); number of re-operations due to MBSE; and mortality.

16.3.2.3 Quality assessment

We specifically addressed the following: completeness of outcome data; selective outcome reporting; definition bias; bias in concepts; bias of assessment; and bias due to confounders.

16.3.2.4 Statistical analysis

Meta-analysis for surgical bleeding events (SBE) and 30 day mortality was done using the Mantel-Haenszel method to estimate the pooled odds ratio. Random effect model was used if the Q statistic χ^2 test for heterogeneity was significant ($p < 0.05$) or $I^2 > 50\%$, if not a fixed effect model was used. If a fixed effect model was used an adjustment of 0.1 was added to events with zero cases, but only in the calculation of the odds ratio for the single study not in the pooled odds ratio. If a random effect model is used this adjustment affects the weighting in the pooled odds ratio estimate and thereby the estimate, zero case studies are therefore excluded in the case of random effect models.
All analysis was done using R 3.0.2 (R Foundation for Statistical computing, Vienna, Austria).

16.3.3 Results

16.3.3.1 Literature review

We identified 137 studies through the search. After the screening process we included five studies [19–23] (See fig 1. for PRISMA flowchart.). All of the identified studies were single-centre retrospective studies with a control group except for one trial that was a two-centre prospective trial with a matched control group [19]. (Table *** gives details of the studies included and data extracted). We also included a study done at our institution where patients were operated <24 hours after discontinuation of therapy [24] We did not identify any Randomized Clinical Trials on the subject.

16.3.3.2 Assessment of bias

The studies were all at risk of several types of bias. Exclusion criteria and participant exclusions were adequately addressed in all six studies. Description on how missing data was handled was only reported in one study [24].
One study [21] did not report on the delay to surgery. Two studies [19,22] had a mean delay to surgery >2 days. Although patients were not discontinued in Clopidogrel or DAPT in any of the studies it could still represent a source of bias.
The issue with studies looking at outcomes related to blood loss is that a large blood loss can be caused by both single events (such as the lesion of an artery during surgery) or by several contributing factors (duration of surgery, blood pressure during surgery, patients inherent coagulation status and many others) that lead to a large blood loss, where Clopidogrel/DAPT is only one of them. The studies all addressed some of these confounders by their exclusion criteria. None of the studies had any strict definitions of surgical bleeding events prior to inclusion, putting them at risk for bias of concepts. Only three [19,22,24] studies reported their transfusion thresholds. One of these studies only measured haemoglobin levels at first, third and seventh postoperative day [19], the other study [22] measured haemoglobin on admission and at day one to three postoperatively. The last study measured haemoglobin on admission and the following three days [24].
Only three studies reported on the use of DVT prophylaxis, stating that all [21,24] or most [22] of the patients in both groups received DVT prophylaxis.
Another risk of bias is that patients in Clopidogrel therapy might receive special attention, e.g. operated by the most experienced surgeon, receiving special attention from the anaesthesiologist during surgery and from the doctors and nursing staff, in the postoperative regimen.

A major source of bias that is not addressed in any of these studies is the question of patient adherence and non-responders to treatment. Non-adherence is reported as high as 1 in 6 patients in the literature [25,26]. This combined with the reported incidence between 6-24% of patients that are non-responders to therapy [9] puts this study at risk bias in selection of subjects, as the patients are not under the effect of Clopidogrel or DAPT at the time of surgery. But all of the studies have a high external validity as the study patients are identical to the target population (patients using Clopidogrel at the time of surgery).

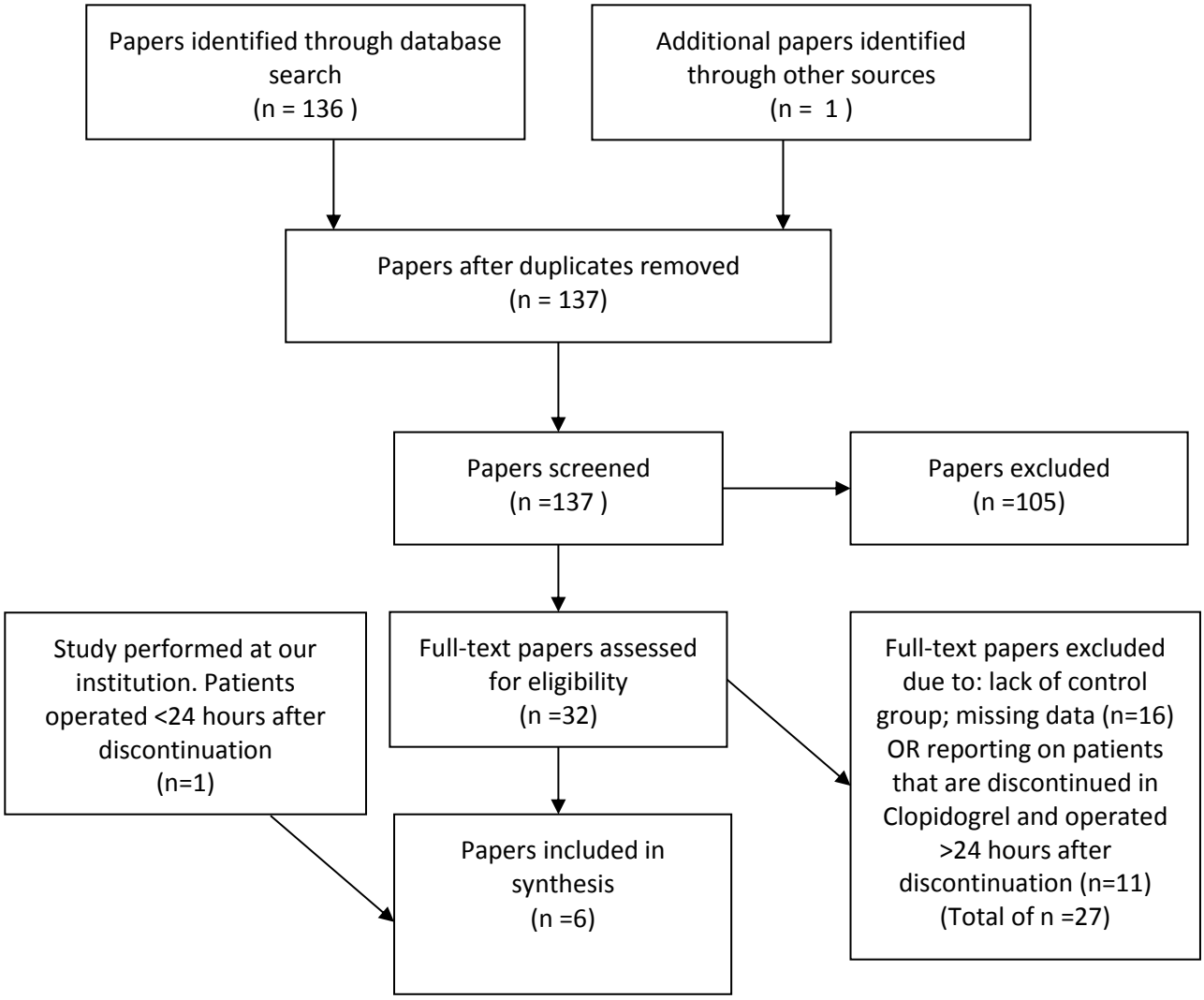

Fig. 1. PRISMA flowchart

16.3.3.3 Characteristics and intervention

A total of six studies were included (see Table 1. for study characteristics). We identified five studies that included patients operated for hip-fractures that were not discontinued in Clopidogrel therapy or DAPT before surgery. All five studies had a control group that did not receive any other antithrombotic medication, except for ASA. We also included a recent study done at our institution where patients were discontinued in therapy but were operated <24 hours after admission and discontinuation, and therefore are assumed to be under full effect of Clopidogrel at the time of surgery. All six studies reported on surgery related bleeding complications, such as hematoma and wound discharge. Five studies report on mortality, of which four report it as 30-day mortality.

The prospective trial by Chechik et al [19] reported on four groups of patients: *No therapy group; Aspirin therapy group; Clopidogrel therapy group;* and *DAPT group*. We only included the *Clopidogrel therapy* group and the *No therapy group* in our results. This trial reported on a mix of hip-fracture operation types. Patients in Clopidogrel or DAPT were included prospectively and patients in the two control groups were matched to these by operation type. They reported no major bleeding events in relation to surgery. They conclude that early surgical intervention without discontinuation of therapy leads to greater perioperative blood loss but otherwise appears safe.

Feely et al [20] conducted a retrospective cohort study with a 2:1 matched control group obtained from an epidemiologic database on a mix of hip-fracture operation types. Patients were matched according to ASA-score. They reported no major bleeding events directly related to surgery. But they did report three (two intra-cerebral and one GI-tract bleeding) and two (GI tract bleeding) bleeding events in the control group and intervention group respectively. They reported no difference in DVT prophylaxis between the two groups. They did a one-year follow up for repeated surgical interventions. They found no difference in perioperative bleeding complications, blood loss or mortality between the two groups. The conclusion was that; “prompt surgical treatment in hip-fracture patients taking Clopidogrel does not compromise perioperative outcomes”.

Hossain et al [21] conducted a retrospective study on hip-fracture patients operated with hemiarthroplasty. The control group was matched by ASA score. There was no significant difference in surgical blood loss or relative risk of receiving a transfusion. Three patients in the Clopidogrel group had postoperative hematomas compared to one patient in the Control group. One patient in the Clopidogrel group had to be re-operated due to hematoma. Infection rates were similar in the two groups. They conclude that their; “data supports the argument for continuing Clopidogrel throughout the perioperative period of hip hemiarthroplasty surgery”. They also emphasise an individualized approach.

Wordsworth et al [23] did a retrospective study on patients operated with a mix of hip-fracture operation types. They reported no significant difference in surgical blood loss, number of transfusions and mortality at one year. There were no incidences of hematoma in the Clopidogrel group. They conclude that; “these patients can be managed by normal protocols…with early surgery.”

Manaqibwala et al [22] did a retrospective study on hip-fracture patients operated with hemiarthroplasty. The control group was not matched to the Clopidogrel group. They found no difference in haemoglobin drop from admission to last measured haemoglobin, in number of transfusions received or all-cause mortality. There was no significant difference in bleeding or wound related complications. They conclude that; “surgery should not be delayed in these patients, and therapy should not be discontinued in the perioperative period…”

Table 1. Characteristics of studies

Author	Year	Operation type	Control group		Number of subjects		Age		ASA-score		Delay to surgery (days)	
			Matched by	Cohort	Clop (n)	No Clop (n)	Clop (n)	No Clop (n)	Clop	No Clop	Clop	No Clop
Tengberg	2015	IMN*		X	36	320	81.1 [9.2]	78.7 [11.9]	1+2: n=15 (41.7%)	1+2: n=226 (70.6%)	0.5 [0.2]	0.6 [0.2]
Manaqibwala	2014	Hemi**		X	15	147	81.3 [10.3]	84.3 [8.8]	3.9 [0.3]	2.9[0.9]	2.3 [2]	1.9 [2.9]
Wordsworth	2013	Mixed	ASA		30	1195	82.8 [8.2] range 62-95	82.3 [9.4] range 19-105	NA	NA	1.2	1.2
Hossain	2013	Hemi**		X	50	52	82.8 [7.3]	83.2 [7.8]	NA	NA	Not reported	
Feely	2013	Mixed	ASA		40	80	82.0 [8.7]	82.3 [8.3]	NA	NA	1.1 [0.7]	1.3[1.3]
Chechik	2011	Mixed	Operation		29	22	82.0[8.0]	82.0[6.0]	2.93[0.65]	2.68[0.89]	2.1 [1.0]	1.8 [1.1]

Author	Transfusions (U)				Surgical Bleeding Event (SBE)		Reoperation due to SBE		Mortality (intervention/control)			
	Clop	No Clop	p-value	Threshold	Clop (n)	No Clop (n)	Clop (n)	No Clop (n)	Clop (n)	No Clop (n)	FU	p-value
Tengberg	3.4 [2.2]	3.0 [2.3]	0.18	<10 g/dl	0	2	0	0	2	23	30 days	0.98
Manaqibwala	0.9[1.1]	0.6[1.4]	0.23	<8 g/dl	1	2	0	0	1	6	30 days	0.24
Wordsworth	0.67[1.11]	0.55[1.05]	0.54	?	0	2	0	0	2	74	30 days	0.71
Hossain	3.96 (0.4-39.6)‡			?	3	1	1	0	Not reported			
Feely	2.1 [2.1]	2.1[3.5]	0.49	?	0	0	0	0	11	23	1 year	0.23
Chechik	1.38[0.98]	1.09[1.38]		<9 g/dl	6	1	0	0	0	0	30 days	NA

Unless stated otherwise, results are reported as mean with [Standard Deviations]; *) IMN=Intramedullary Nail; **) Hemi=Hemiarthroplasty; ‡) Reported as Adjusted Risk Ratio

We conducted a retrospective study [24] on hip-fracture patients operated with an intramedullary nail. The control group was not matched to the Clopidogrel group, but included consecutively within the inclusion period. There was no significant difference in Surgical Blood Loss, Total Blood Loss or events of Massive Transfusion (defined as >10 units of RBC in <24 hours). Our conclusion was that "…we would recommend that hip-fracture surgery should be conducted without delay and without withdrawal of Clopidogrel therapy or DAPT".

16.3.3.4 Analysis of results

The reporting of results across studies is heterogeneous. Number of transfusions are reported as mean (SD) in four of five studies, but is not comparable as only two of the studies report transfusion thresholds. These two studies have different thresholds, and also measure haemoglobin levels at different times postoperatively. Mortality is comparable in the four studies reporting 30-day mortality. We created a category called Surgical Bleeding Events (SBE) and included reports of haematoma and wound discharge in this category. There are no reports in any of the studies on other types of surgery related bleeding events beyond these two types. All but one study report on wound infection, but we did not include this in the SBE category as wound infection is a multifactorial event not necessarily related to wound discharge or haematoma. There were no reports in any of the studies of patients who had an excessive and/or uncontrollable blood loss during surgery.

We did a meta-analysis of SBE and 30-day mortality in the relevant studies. In both SBE and the 30 day mortality the heterogeneity test and I^2 did not suggest the use of a random effects model therefore the results are taken from the fixed effect model. However the random effects model gives the same results as the fixed. A statistical significant larger OR of 3.64 (95%CI = 1.04 — 12.78, p = 0.044) for SBE, and a statistical non-significant OR of 0.99 (95%CI = 0.39 — 2.53, p = 0.986) for 30 mortality.

Results are shown in fig 2 and 3.

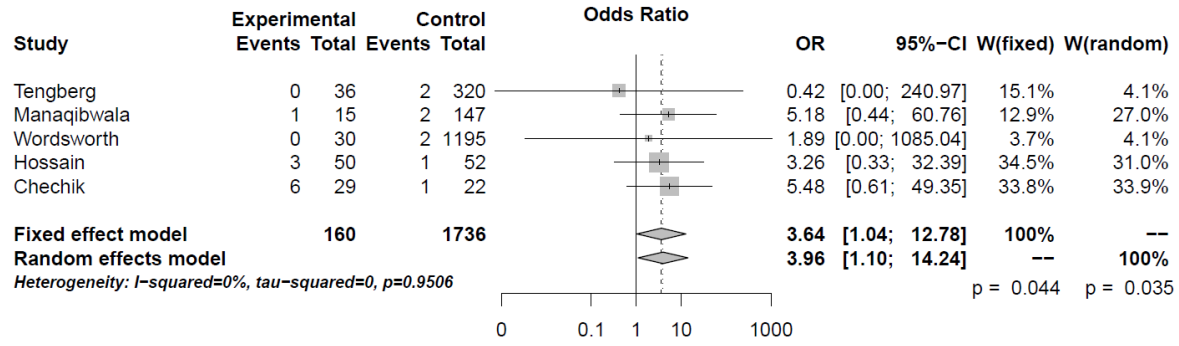

Fig. 2. Results of Meta-Analysis of Surgical Bleeding Events (SBE).

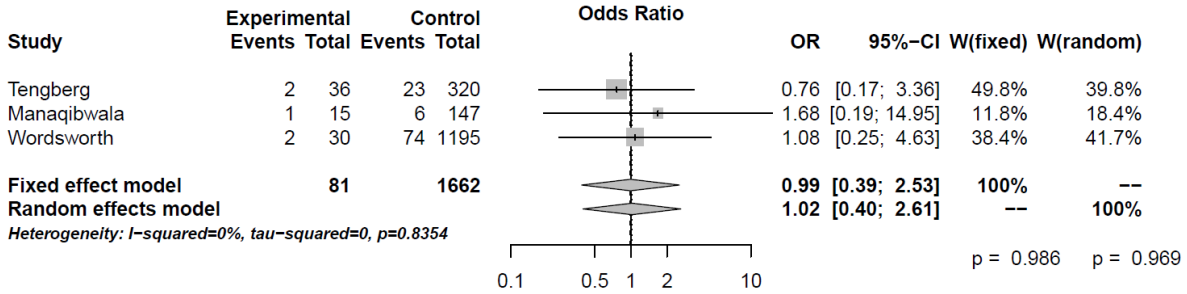

Fig. 3. Results of Meta-analysis of 30-day mortality. The study by Chechik et al. was also included but had 0 events in both groups.

16.3.4 Discussion

We have identified six studies including a total of 200 patients in Clopidogrel therapy or DAPT operated for hip-fractures without pre-operative discontinuation of therapy or where surgery was performed <24 hours after discontinuation of therapy.

We found a statistically significant increased OR for surgical complications that could be directly related to increased bleeding (SBE) in the form of wound discharge or haematoma in the Clopidogrel group. There is a risk of definition bias for this outcome as they are reported based on assessment of the individual surgeon. The question is how clinically relevant these complications are? And what is the severity of these complications compared to the complications associated with discontinuation of therapy? Only one patient was re-operated as a consequence of these complications.

Data on surgical or other measures of total blood loss and transfusions were too heterogeneous to do pooled analysis, but all the studies reported non-significant or no difference between intervention and control groups. More importantly there were no incidences of patients with uncontrollable bleeding during or after surgery. And there were no cases of fatalities directly related to excessive surgical bleeding. Our meta-analysis did not find an increased OR for 30-day mortality in the Clopidogrel group.

With these findings we have demonstrated that the fear of excessive, irreversible and uncontrollable surgical bleeding in this group of patients may be exaggerated. This aligns well with the recommendations of several literature reviews and published guidelines on the subject. All these guidelines state that aspirin should never be discontinued, and that discontinuation of Clopidogrel therapy should be reserved for patients at risk of bleeding in a closed space (e.g. neurosurgery, retro-bulbar eye surgery). The decision to discontinue therapy should always be taken after consultation with a cardiologist, and in the case of recent coronary stent placement (3-12 months depending on stent type), treatment should never be discontinued. The practice of so-called “bridging” with different forms of anti-thrombins is not recommended as an alternative [6,7,9,14,17,27].

The complication of excessive blood loss happens in a controlled environment where steps can be taken to reduce the blood loss and the negative effects of it. In case of uncontrollable bleeding balanced component therapy can be used to provide haemostasis. This is possible due to the relatively short half-life of Clopidogrel at 4 hours [9,14].
A thromboembolic complication following surgery can occur after discharge from hospital. It has more severe consequences and even if it is not instantly fatal, its effects are largely irreversible.

Based on our findings we would recommend that hip-fracture surgery should be carried out without delay and without discontinuation of Clopidogrel or DAPT before surgery. Larger prospective observational studies should be carried out to further identify the risk factors and predictors of morbidity and mortality in urgent surgery in this high risk population. Such studies should be designed to make inferences on non-inferiority and ideally be carried out as collaboration between cardiologists, anaesthesiologists and orthopaedic surgeons.

16.3.5 Funding

No external funding was received for this study.

16.3.6 Literature

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16.4 Study IV

Low incidence of pre-operative coagulopathies measured by Thrombelastography® (TEG®) in hip-fracture patients.

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Abstract

*Background:*Hip-fracture patients sustain a large Total Blood Loss (TBL), both in relation to the fracture itself and the following surgery. Viscoelastic Hemostatic Assays (VHA) such as Thrombelastography® (TEG) has been used to assess coagulopathies in trauma patients and proposed as a useful tool to guide transfusion therapy.

Materials and Methods: We conducted a prospective blinded descriptive observational study with 179 consecutive hip-fracture patients. A TEG analysis was performed on admission to determine the incidence of coagulopathies. We did an analysis of the usefulness of TEG as a tool to predict TBL in the population.

Results: We found 25 patients (13.9%) with coagulopathies as detectable by TEG in our population. We were not able to predict TBL with the use of TEG.

Conclusion: Given the low rate of coagulopathies detectable by TEG and the inability to predict TBL we cannot recommend TEG as a standard screening test on admission for hip-fracture patients.

16.4.1 Introduction

16.4.1.1 Background/Rationale

Postoperative anemia necessitating transfusion and a hemoglobin level below 8 g per dL, in hip-fracture patients, are both associated with an increased mortality [1,2]. Controversy remains on the benefits and indications for transfusion in this group of patients [3–6]. This naturally leads to a search for new ways to reduce the blood loss and assess optimal use of transfusions.

One strategy that have been successful in patients with massive hemorrhage and in trauma patients is the use of Point Of Care (POC) testing of coagulation status in these patients, using Viscoelastic Hemostatic Assays (VHA) such as Thrombelastography® (TEG) and Rotation Thrombelastometry® (ROTEM). Conventional plasma based coagulation screening tests including PT and aPTT have proven to be poor measures for monitoring coagulation status. There is currently no viable method of identifying patients at risk of transfusion. The on admission hemoglobin level has been shown to be falsely reassuring [7]. VHA has successfully been used to assess coagulopathies in trauma patients [8,9] and has proven superior to guide transfusion therapy, reduce the blood loss and the transfusion requirements in cardiac surgery, vascular surgery, liver transplantation and trauma surgery compared to the conventional tests [9–14]. It has yet to demonstrate a positive effect on morbidity or mortality according to a recent Cochrane review on the subject [14]. VHA based algorithms for both TEG and ROTEM have been proposed, but these are not validated in large randomized clinical trials [13,15].

Hip-fracture patients suffer large blood losses, both as a consequence of the fracture itself and the following surgery. VHA may also have a place as a transfusion guide in this group of patients who have many comorbidities and frequent use of anticoagulation medicine [16,17].

16.4.1.2 Objectives

Our main objectives were a simple determination of distribution of five of the TEG variables (R, Angle, MA and LY30) in a geriatric population admitted with a hip-fracture. We hypothesized that these values would be able to predict the patients Total Blood Loss (TBL) [18]. We also hypothesized that many of these patients would have coagulopathies detectable by TEG analysis on admission.

16.4.2 Methods

16.4.2.1 Study design

We did a prospective observational cohort study of hip-fracture patients submitted to Thrombelastography® (TEG®) analysis upon admission. The study was designed, performed and is reported in accordance with the STROBE-statement [19]. We conducted TEG on admission on 200 consecutive hip-fracture patients, and compared results of the TEG analysis with the blood loss of the patients. Clinical staff was blinded to the results of the TEG analysis in the study period. Blood loss was assessed as Total Blood Loss (TBL) as described by Foss et al [18]. The study was conducted in accordance with the declaration of Helsinki, approved by the local committee on health research ethics (ID: H-2-2013-FSP09) and registered at Clinicaltrials.org (ID: NCT02297061).

16.4.2.2 Setting
Designed as a single-center study conducted at Copenhagen University Hospital Hvidovre. Starting in December 2013 and planned to run until we had included 200 patients. Follow up was for a 90 day period. Data collection was conducted as part of the department standard and recorded into the relevant clinical databases at the hospital. Data was retrieved from these databases by the principal investigator and put into a dedicated database.

16.4.2.3 Participants
Participants were all consecutive patients admitted for hip-fractures at Copenhagen University Hospital Hvidovre during the study period and until we had reached our target of 200 included patients. No exclusion criteria were deemed necessary as this was not an interventional study. All results of the TEG analysis were blinded to all clinical staff and research staff until the conclusion of the study.

16.4.2.4 Variables
Five of the TEG variables (R, K, Angle, MA and LY30) were recorded and compared to the reference ranges used in our setting (R 4-9 min; Angle 55-78°; MA 51-69 mm and Ly30<4%) and to the reference ranges described by Macafee et al [20].
Our primary outcome was the association between the TEG variables and the TBL calculated from patient weight, height, gender and number of transfusion from day 0 to 4, hemoglobin concentration on admission and on the 3rd postoperative day, if available. If 3rd day hemoglobin was not available, the last available measurement was used [18]. We also recorded; number of transfusions (Red Blood Cell (RBC); Fresh Frozen Plasma (FFP) and Platelets), number of patients receiving >10 Units of RBC within a 24 hour period (massive transfusion [21]), surgical blood loss, mortality at 90 days postoperatively, antithrombotic treatment on admission (type of drug), comorbidities that may affect coagulation, International Normalized Ratio (INR) on admission and Platelet count on admission.

16.4.2.5 Data sources
Blood samples were taken from patients on admission in a 3 ml citrated coagulation blood bottle, and transported directly to analysis. Before analysis they were injected into kaolin tubes by an experienced operator. TEG was measured using; Thrombelastograph® 5000, Haemoscope Corp. Niles IL USA. Weight and height was assessed by the admitting doctor. Number of transfusions between day 0 and 3 were retrieved from the database of the local blood bank that delivers all blood products used in our department. Surgical Blood Loss (SBL) was registered by the operating room personnel and recorded by the operating surgeon in the patient record. 90 day mortality was registered from the “Central Persons Registry” (*CPR registeret*) that holds information on mortality of all national citizens. All clinical data was registered in the relevant clinical databases and later retrieved and put into a dedicated database.

16.4.2.6 Study size
The study size was arrived at by a qualified estimate between the authors, as there were no previous studies to base any power estimates on. A sample size of 200 would, based on previous data from our institution, allow for approximately 100 extra-capsular and 100 intra-capsular fractures.

16.4.2.7 Statistical methods

The relationship between the TEG variables and TBL was analyzed using linear regression models with R; MA; LY30; Angle; fracture type (Extra- or Intra-capsular); antiplatelet medicine (ASA and ADP-RI); other anticoagulant medicine (VKA, Pradaxa, Xarelto and others); and SBL. An interaction between fracture type and the TEG variables was also included to allow different effects of the TEG variables for each fracture type. Univariate analysis of TBL was done using two-sample t-test or anova for the variables included in the linear regression model.
Test for the effect of the TEG parameter was done using the type III SS F test. Statistical significance was defined as p-values of less than 0.05. All analysis was done using R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria)

16.4.3 Results

16.4.3.1 Participants

In a period from December 2013 to April 2014 there were 200 patients eligible for study inclusion. 21 patients did not have a TEG analysis conducted on admission (n=12) or their TEG analysis was flawed (n=9), leaving 179 patients in the final analysis.

16.4.3.2 Descriptive data

Characteristics of the study participants are summarized in Table 1. Data was missing in; 10 patients for surgical blood loos, 2 patients for INR on admission and 2 patients for platelets on admission. LY30 measurement was flawed in one patient.

16.4.3.3 Outcome data

The TEG variables were all normally distributed. They are presented in histograms (Fig 1.) with marking lines at their normal level cut off points. Histogram plots were grouped in three categories: Patients receiving antithrombotic medication (ADP-Receptor inhibitors (ADP-RI), Direct Thrombin inhibitors, direct factor Xa inhibitors and Vitamin K-antagonists (VKA)); patients receiving acetylsalicylic acid (ASA); and patients that did not receive any of these medications.

There were no incidences of elevated LY30 combined with elevated MA or angle, as a sign of reactive hyper-fibrinolysis. A total of 25 patients had values outside the normal reference range. 2 patients had more than one value outside the normal reference range. Of the 9 patients with prolonged R time (>9 min.) 7 took some form of anticoagulation medicine that could affect their R time (4 were in direct Thrombin inhibitor treatment; 2 were in VKA; and 1 were in Heparin treatment). One patient with lowered angle took ASA. Of the 3 patients with lowered MA, one had cirrhosis and another was in treatment with a direct factor Xa inhibitor with atrial fibrillation as indication, this patient also had an affected LY30. Among the 12 patients with LY30>4%, 3 took some form of anticoagulation medicine that could affect clot lysis (2 in ADP-RI; and 1 in direct factor Xa inhibitor treatment). No other relevant risk factors could be identified in the remaining patients with TEG values outside reference range.

5 patients had an INR value > 3 on admission. All of these patients were VKA users. Only one of these patients had a TEG value outside reference range (R=9.2 min.). 2 patients had a platelet count <100x10^9/l. One of these patients was the patient with cirrhosis who also had lowered MA (MA= 43.7mm).

Mortality at 90 days follow-up was 24% (n=6) for the patients with TEG values outside reference range.

Table 1

Sex	M	55 (30.7%)
	F	124 (69.3%)
Age (yrs.)	mean	79.1 [11.9]
ASA-score	1	17 (9.5%)
	2	85 (47.5%)
	3	70 (39.1%)
	4	7 (3.9%)
Operation	Parallel Screws/Pins	27 (15.1%)
	Hemiarthoplasty	63 (35.2%)
	SHS	17 (9.5%)
	IMN short	51 (28.5%)
	IMN long	21 (11.7%)
Anticoagulation medicine	none	105 (58.7%)
	ADP-RI	18 (10.1%)
	Pradaxa + Xarelto	10 (5.6%)
	VKA	12 (6.7%)
	ASA	31 (17.3%)
	other	3 (1.7%)
Patients with one or more vaules outside TEG reference range	n	25 (13.9%)
R> 9 min.	n	9 (5.0%)
angle< 55°	n	3 (1.6%)
MA< 51 mm	n	3 (1.6%)
LY30> 4%	n	12 (6.7%)
LY30> 8%	n	0
90 day mortality	n	35 (19.6%)
Transfusions (RBC)	mean	2.1 [1.9]
Received RBC transfusion	n	129
Received FFP transfusion	n	12
Received platelet transfusion	n	2
Received >10 RBC in 24 hours	n	2
Surgical Blood Loss (SBL)	mean	278.6 [234.1]
Total Blood Loss (TBL)	mean	1597 [904.3]

Means are reported with [Standard Deviation];SHS=Sliding Hip Screw; IMN=Intramedullary Nail; ADP-RI=ADP Receptor inhibitors; VKA=Vitamin K-antagonists; ASA=Acetylsalicylic acid; RBC=Red Blood Cell; FFP=Fresh Frozen Plasma.

Table 2: Univariate analysis

Variable	Mean Change	Lower 95%CI	Upper 95%CI	p-value
Extra Capsular Fracture	316.92	-13.8	647.6	0.060
Medicin - Platelet Inhibitors	292.948	-12.4	598.3	0.165*
Medicin - Other antithrombotic medication	141.417	-251.2	534	
R	32.105	-44.1	108.3	0.407
MA	7.271	-16.8	31.3	0.551
LY30	-2.787	-79.6	74.1	0.943
Angle	16.619	-10.3	43.5	0.224
Surgical Blood Loss (SBL)	1.62	1.1	2.1	<0.001

***Simultaneous test**

Table 3: Estimate of effect by variables

Variable	Effect	Lower CI 95%	Upper CI 95%	p value
R	59,296	-36,868	155,461	0,225
MA	-20,198	-56,955	16,558	0,279
LY30	15,977	-64,655	96,61	0,696
Angle	32,291	-9,755	74,338	0,131
Intra-Capsular Fracture	-1446,944	-7275,002	4381,113	0,625
Platelet Inhibitors	389,704	97,863	681,546	0,009
Other antithrombotic medication	121,259	-285,202	527,719	0,556
Surgical Blood Loss	1,638	1,089	2,187	<0.001
Fracture Type *	-	-	-	-
R	21,705	-247,473	290,882	0,874
MA	31,906	-45,886	109,697	0,419
LY30	-105,117	-324,216	113,981	0,345
Angle	-11,419	-105,21	82,372	0,81

***) Reference fracture type=Extra-Capsular**

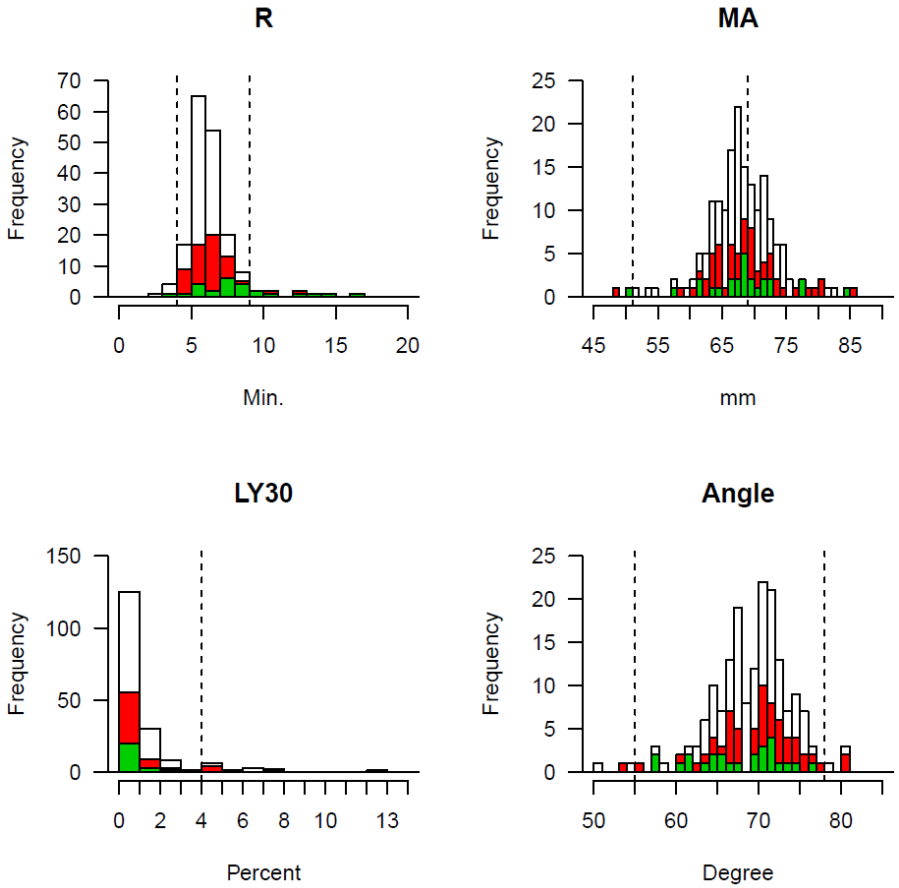

Fig. 1. Histograms of TEG variables with cut-off points for reference ranges. Red color= antiplatelet medicine (ASA and ADP-RI); Green color=other anticoagulation medicine (see table 1); White color=no antithrombotic medication.

16.4.4 Main results

16.4.4.1 Prediction of TBL

None of the individual TEG variables were able to predict the TBL. The first model showed very poor agreements between the measured TBL and the model predicted TBL, because of this we focused on the more complex model, which showed better predictions (See fig 2.). None of the TEG variables had a statistically significant effect.

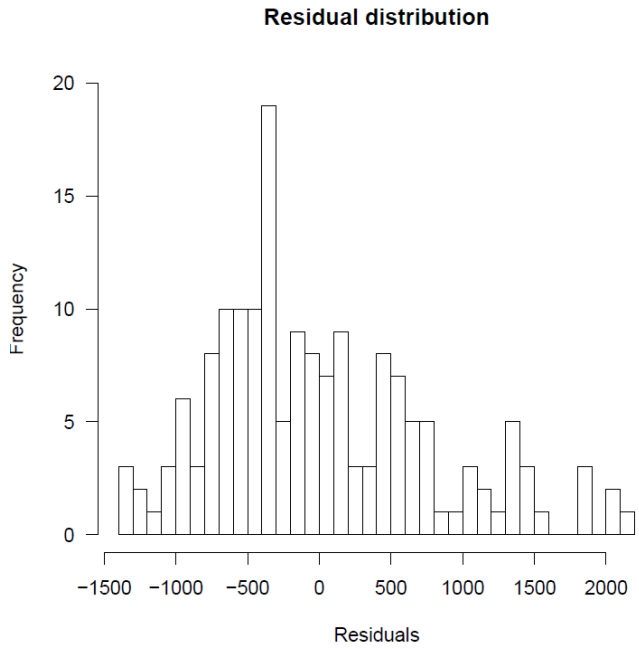

Fig. 2. Difference between predicted and calculated blood loss (residuals) for all patients.

16.4.5 Discussion

16.4.5.1 Key results

We found normally distributed values for all four TEG variables with a low proportion of patients with TEG values outside reference range. Predominantly prolonged R value and elevated LY30 value. This indicates that the incidence of coagulopathies detectable by TEG in this population is relatively low. We were not able to find any significant correlation between TEG values on admission and TBL.

16.4.5.2 Limitations

The prediction of TBL by TEG is limited by the many factors that contribute to TBL. Several of these are not possible to predict from patients coagulation status on admission. A major confounder is surgical technique and bleeding events during surgery that are not directly related to patient coagulation status on admission. Platelet function can be measured by TEG, but specific drug induced platelet inhibition cannot which could also affect the potential for TEG to predict TBL in this group of patients with a high incidence of platelet inhibitor use.

In our study we primarily found prolonged R value and elevated LY30. Only a total of 6 patients had lowered MA or angle. A recent study suggests that R and LY30 values are the least reproducible of the five TEG values [22]. If this can be translated to our study we might over- or under-estimate the amount of coagulopathies detectable by TEG.

We only did a single TEG measurement on admission and are not able to control for changes in coagulation during or after surgery

16.4.5.3 Interpretation

Our results indicate that there is a low incidence of coagulopathies detectable by TEG on admission in a population with mixed types of hip-fractures. We have only identified one other study on patients with hip-fractures where TEG was performed on admission [23]. This study does not report on values outside reference range on admission.

We were not able to predict which patients were at risk of large TBL from the TEG analysis. A large study on 321 cardiac surgery patients [24] used ROTEM and could not predict the at-risk patient. Another study on 434 cardiac surgery patients identified the MA value (clot strength) as a predictor of increased blood loos when it was implemented in a model that also stratified for patient and surgery related variables [25]. The characteristics for these studies are that several VHA measurements are made and some of these are made during surgery. Our present data cannot exclude the possibility that coagulopathies are induced intra or postoperatively secondary to major blood loss, which should be examined in future studies. Also, we have not specifically measured platelet inhibition and the clinical application of measures of drug induced platelet dysfunction remains to be investigated in this patient population.

16.4.5.4 Generalizability

Our results have a high external validity as they were performed on a population that is identical to our target population, in a clinical setting with no exclusion criteria.

16.4.6 Conclusion

Based on our findings we would not recommend TEG as a standard on-admission analysis in hip-fracture patients. The incidence of coagulopathies detectable by TEG is too low to justify this relatively costly test as an on-admission screening tool. TEG analysis should be reserved for patients who are at an increased risk of large blood losses, due to medication, co-morbidities or clinical suspicion of coagulopathy. Ideally this should be done in a protocolled manner as TEG has not been validated for this patient group.
Whether TEG in the intra- and post-operative phase can guide therapy in hip-fracture patients with extensive intraoperative blood loss remains to be investigated.

16.4.7 Funding

This study received no external funding.

16.4.8 Literature

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Blood loss in hip-fractures

This declaration concerns the following article:
Low incidence of pre-operative coagulopathies measured by Thrombelastography® (TEG®) in hip-fracture patients.

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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26/3 15	Thomas Kallemose	MSc in statistics	

Signature of the PhD student and the principal supervisor:	
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Title of PhD thesis:
Blood loss in hip-fractures

This declaration concerns the following article:
Tranexamic Acid (TXA) reduces blood loss in patients with extra-capsular hip fractures; results of a randomized controlled trial.

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	C
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Title of PhD thesis:
Blood loss in hip-fractures

This declaration concerns the following article:
The case for continuing Clopidogrel® therapy during hip-fracture surgery. Results of a systematic review.

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
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Title of PhD thesis:
Blood loss in hip-fractures

This declaration concerns the following article:
Hip-Fracture Surgery on patients in Clopidogrel therapy is not associated with high risk of major blood loss

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
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