ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
ΘΡΟΜΒΩΣΗ ΚΑΙ ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ

Μεταπτυχιακή Διπλωματική Εργασία

" ΠΕΡΙΕΓΧΕΙΡΗΤΙΚΟΣ ΑΙΜΟΡΡΑΓΙΚΟΣ ΚΙΝΔΥΝΟΣ ΣΕ ΑΣΘΕΝΕΙΣ ΠΟΥ ΛΑΜΒΑΝΟΥΝ ΝΤΑΜΠΙΓΚΑΤΡΑΝΗ ΣΥΓΚΡΙΤΙΚΑ ΜΕ ΑΣΘΕΝΕΙΣ ΠΟΥ ΔΕΝ ΛΑΜΒΑΝΟΥΝ DOACS: ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΤΥΧΑΙΟΠΟΙΗΜΕΝΩΝ ΜΕΛΕΤΩΝ"

Υπό

Απόστολου – Αλκιβιάδη Μένη

Ειδικευόμενου Αναισθησιολογίας

Υπεβλήθη για την εκπλήρωση μέρους των
απαιτήσεων για την απόκτηση του
Διπλώματος Μεταπτυχιακών Σπουδών
«Θρόμβωση και Αντιθρομβωτική Αγωγή»

Λάρισα, 2023

Επιβλέπων:

Αρναούτογλου Ελένη, Καθηγήτρια *Αναισθησιολογίας, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας*

Τριμελής Εξεταστική Επιτροπή:

1. Αρναούτογλου Ε.
2. Νταλούκα Μ.
3. Μπαρέκα Μ.

Αναπληρωματικό μέλος:

Σταμούλης Κ.

Τίτλος εργασίας στα αγγλικά:

Perioperative bleeding risk in patients taking Dabigatran compared with patients not on a Direct Oral Anticoagulant: A systematic review of randomized clinical trials.

Περίληψη

Περιεγχειρητικός αιμορραγικός κίνδυνος σε ασθενείς που λαμβάνουν Νταμπιγκατράνη συγκριτικά με ασθενείς που δεν λαμβάνουν DOACS: Συστηματική ανασκόπηση τυχαιοποιημένων μελετών

Εισαγωγή: Σε αυτή την συστηματική ανασκόπηση ο σκοπός ήταν να μελετηθεί και να εκτιμηθεί ο σχετιζόμενος με την νταμπιγκατράνη περιεγχειρητικός αιμορραγικός κίνδυνος.

Μεθοδολογία: Οι μελέτες που χρησιμοποιήθηκαν ήταν τυχαιοποιημένες κλινικές μελέτες, οι οποίες συνέκριναν την νταμπιγκατράνη (χωρίς συνδυασμό με άλλα αντιπηκτικά ή αντιαιμοπεταλιακά φάρμακα) με μη – DOACs στην περιεγχειρητική περίοδο. Πραγματοποιήθηκε αναζήτηση στο PubMed και Scopus, αξιοποιώντας μελέτες από τον Ιανουάριο του 2002 μέχρι και τον Μάρτιο του 2023. Για την αξιολόγηση της μεθοδολογικής ποιότητας χρησιμοποιήθηκε η δεύτερη έκδοση του Cochrane risk-of-bias tool.

Αποτελέσματα: Η παρούσα συστηματική ανασκόπηση περιλαμβάνει 9 μελέτες με συνολικό πληθυσμό 17.912 ασθενών. Πέντε από τις μελέτες αξιολόγησαν το αιμορραγικό ρίσκο της νταμπιγκατράνης σε σχέση με την ενοξαπαρίνη για την πρόληψη της μετεγχειρητικής φλεβικής θρομβοεμβολικής νόσου ύστερα από ολική αρθροπλαστική ισχίου/γόνατος (πληθυσμός 12.097 ασθενείς), 3 μελέτες αξιολόγησαν το περιεπεμβατικό αιμορραγικό ρίσκο σε σχέση με την βαρφαρίνη σε ασθενείς με κολπική μαρμαρυγή οι οποίοι επρόκειτο να υποβληθούν σε θεραπεία κατάλυσης (πληθυσμός 1224 ασθενείς) και μια μελέτη αξιολόγησε το αιμορραγικό ρίσκο σε ασθενείς που λαμβάνουν νταμπιγκατράνη σε σχέση με ασθενείς που λαμβάνουν βαρφαρίνη και πρόκειται να υποβληθούν σε χειρουργική επέμβαση (σύνολο 4591 ασθενείς). Η νταμπιγκατράνη ενέχει τον ίδιο αιμορραγικό κίνδυνο με την ενοξαπαρίνη για την πρόληψη της φλεβικής θρομβοεμβολικής νόσου ύστερα από ολική αρθροπλαστική ισχίου/γόνατος, τον ίδιο αιμορραγικό κίνδυνο σε σχέση με την βαρφαρίνη σε ένα γενικό περιεγχειρητικό πλαίσιο για ασθενείς με κολπική μαρμαρυγή και χαμηλότερο αιμορραγικό κίνδυνο σε σχέση με την βαρφαρίνη σε ασθενείς που υποβάλλονται σε θεραπεία κατάλυσης για κολπική μαρμαρυγή.

Συμπέρασμα: Βάση της πρόσφατης βιβλιογραφίας η νταμπιγκατράνη ενέχει χαμηλότερο αιμορραγικό κίνδυνο σε σχέση με την βαρφαρίνη σε ασθενείς με κολπική μαρμαρυγή που πρόκειται να υποβληθούν σε θεραπεία κατάλυσης και τον ίδιο αιμορραγικό κίνδυνο σε ασθενείς που λαμβάνουν βαρφαρίνη για κολπική μαρμαρυγή και πρόκειται να υποβληθούν σε χειρουργείο ή σε ασθενείς που λαμβάνουν ενοξαπαρίνη για πρόληψη της φλεβικής θρομβοεμβολικής νόσου μετά από ολική αρθροπλαστική γόνατος/ισχίου.

Λέξεις – κλειδιά: Νταμπιγκατράνη, Αιμορραγικό ρίσκο, Περιεγχειρητική περίοδος, νεότερα από του στόματος αντιπηκτικά

Abstract

Perioperative bleeding risk in patients taking Dabigatran compared with patients not on a Direct Oral Anticoagulant: A systematic review of randomized clinical trials.

Background: In this systematic review the aim was to study and assess the bleeding risk associated with dabigatran etexilate in the perioperative and periprocedural setting.

Methods: Studies that were included were randomized clinical trials, comparing dabigatran (not combined with other antithrombotic or antiplatelet medication) with non-direct oral anticoagulants in the perioperative period. A search was conducted in PubMed and Scopus, utilizing studies for January 2002 to March 2023. The tool used for the evaluation of the risk of bias was the Version 2 of the Cochrane risk-of-bias tool.

Results: The present review included 9 studies with a combined population of 17.912 patients. Five of these studies evaluated the bleeding risk of dabigatran compared to enoxaparin when used for the prevention of postoperative venous thromboembolism after total hip/knee replacement (combined population of 12.097 patients), 3 studies assessed the periprocedural bleeding risk in patients with atrial fibrillation undergoing ablation compared with warfarin (combined population of 1224 patients) and 1 study investigated dabigatran-related bleeding risk in patients with atrial fibrillation in the general perioperative setting using warfarin as a comparator (4591 patients). Dabigatran poses the same bleeding risk as enoxaparin for the prevention of postoperative venous thromboembolism, the same bleeding risk as warfarin in the general perioperative setting and finally a lower bleeding risk compared to warfarin in population undergoing ablation for atrial fibrillation.

Conclusion: Based on the current available literature dabigatran poses a lower bleeding risk in patients scheduled for ablation for atrial fibrillation and the same bleeding risk in patients receiving it for atrial fibrillation when scheduled for surgery or for venous thromboembolism prophylaxis after total hip/knee replacement compared with enoxaparin.

Key-Words: Dabigatran, bleeding risk, direct oral anticoagulants, perioperative

Index

Chapter 1 Introduction

1.1. Perioperative bleeding risk

Perioperative bleeding risk is the sum of patient and surgery related bleeding risk factors. The International Society of Thrombosis and Hemostasis has recommended a classification of surgery related bleeding risk in minor, low/moderate and high bleeding risk surgery[1] (Table 1.). The goal of implementing such a classification was to facilitate decision making related to the discontinuation of anticoagulation treatment based on the bleeding risk. For high bleeding procedures/surgeries the recommendation is to interrupt anticoagulants for 4-5 half-times, so that there is no residual anticoagulant action, for low/moderate bleeding risk surgeries/procedures to interrupt anticoagulants for 2-3 half times, as a minor residual anticoagulant action is acceptable and for minor bleeding risk surgeries/procedures the interruption is only for the day of surgery. However, this classification is based on data mainly from small observational studies or case series and is mainly used in clinical trials. Therefore, the majority of the recommendations for the perioperative and periprocedural management of anticoagulants are expert opinions [2].

The patient related bleeding risk factors are multiple[2,3] (Table 2.). There are various scores that are used to predict bleeding, however these are used for patients with atrial fibrillation on anticoagulants[4–6]. Furthermore, due to their low predictive value[2], they are not recommended in the official guidelines.

1.2. Pharmacokinetics and Pharmacodynamics

1.2.1. Dabigatran

Mechanism of action

Dabigatran inhibits thrombin in a direct, competitive and reversible way. Thrombin is inhibited by dabigatran either in its free form or when bound to fibrin. Moreover, dabigatran inhibits thrombin-induced platelet aggregation, thereby preventing thrombus formation[7].

Pharmacokinetics & Pharmacodynamics[7]

Dabigatran etexilate is hydrolyzed to dabigatran in the liver and plasma and the reaction is catalyzed by an esterase. Healthy volunteers were administered doses ranging from 10 to 400 mg once daily or 50 to 400 mg three times daily for 6 days the maximum concentration was reached within 2 hours. The area under the plasma concentration curve and maximum concentration increase in dose-dependent manner, thus dabigatran exhibits linera pharmacokinetics[8]. The bioavailability of dabigatran is at ~6.5%. In the first postoperative hours, dabigatran presents a slower

High bleeding risk procedures (30-d risk of major bleed >2%)	Major surgery with extensive tissue injury Cancer surgery, especially solid tumor resection Major orthopaedic surgery, including shoulder replacement surgery Reconstructive plastic surgery Urologic or gastrointestinal surgery, especially anastomosis surgery Transurethral prostate resection, bladder resection, or tumor ablation Nephrectomy, kidney biopsy Colonic polyp resection Bowel resection Percutaneous endoscopic gastrotomy (PEG) placement, endoscopic retrograde cholangiopancreatography (ERCP) Surgery in highly vascular organs (kidneys, liver, spleen) Cardiac, intracranial, or spinal surgery Any major operation (procedure duration >45 min) Neuraxial anaesthesia
Low/moderate bleeding risk proceduresc (30-d risk of major bleed 0%-2%)	Arthroscopy Cutaneous/lymph node biopsies Foot/hand surgery Coronary angiography Gastrointestinal endoscopy +/− biopsy Colonoscopy +/− biopsy Abdominal hysterectomy Laparoscopic cholecystectomy Abdominal hernia repair Hemorrhoidal surgery Bronchoscopy +/− biopsy Epidural injections
Minimal bleeding risk procedures (30-d risk of major bleed ~0%)	Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi) Opthalmological (cataract) procedures Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings Pacemaker or cardioverter-defibrillator device implantation

Table 1 Bleeding risk per procedure

Hypertension
Abnormal renal function
Abnormal liver function
Prior Stroke
History of or predisposition to (anemia) major bleeding
Labile INR
Elderly >65 years old
Concomitant use of an antiplatelet agent or nonsteroidal anti-inflammatory drug
Alcohol or drug usage history (~8 drinks/week)
Prior bleed event within 3 months (including intracranial hemorrhagic)
Quantitative or qualitative platelet abnormality
INR above the therapeutic range at the time of the procedure (VKA)
Bleed history from previous bridging
Bleed history with similar procedure

Table 2 Increased bleeding risk patient related factors.

absorption rate compared to healthy volunteers, with a smoother plasma concentration profile without high peak plasma concentrations. However, during the postoperative period, the high peak plasma concentrations are reached 6 hours after drug administration. Possible contributing factors are anesthesia, gastrointestinal paresis, and effects form the surgery per se. This phenomenon is described only on the first day with the dabigatran pharmacokinetics returning to normal in the subsequent days. Concomitant consumption of food does not intervene with bioavailability however it increases the time to maximum concentration by 2h. Dabigatran etexilate is provided as hard coated pills. If the coat is removed, then the oral bioavailability increases by 75% after the administration of a single dose and by 37% when steady state is established. The distribution volume of dabigatran is approximately 60-70 L, with low plasma protein binding. Dabigatran is eliminated mainly via renal excretion with a clearance of approximately 100ml/min. Dabigatran has a terminal half-life between 12h and14h following continuous administration.

Dabigatran's anticoagulant effect correlates with plasma concentration. Various laboratory indices, such as activated partial thromboplastin time (aPTT), thrombin time (PT) and ecarin clotting time are prolonged by dabigatran. The diluted thrombin time can be used to provide an estimate of dabigatran concentrations. Normal values of thrombin time exclude the

presence of the drug.[9] An aPTT value in the normal range does not exclude therapeutic levels it, however, excludes supratherapeutic levels. It is not recommended to use the International normalized ratio (INR), as it is an unreliable indicator in patients treated with dabigatran.

1.2.2. Warfarin

Mechanism of action

Warfarin is a Vitamin K antagonist that inhibits the vitamin K dependent factors II, VII, IX, X and is also active against the anticoagulant proteins C and S. Warfarin acts as an inhibitor that interrupts the recycling of vitamin K from vitamin K epoxide.[10]

Pharmacokinetics & Pharmacodynamics

Warfarin is a racemic mixture of two optical isomers, stereoisomers R and S. It has a high-water solubility, a rapid gastrointestinal absorption, a high bioavailability and achieves peak concentration in plasma in approximately 90 minutes. It's half-life (t½) is between 36 and 24 hours, it is protein bound mainly to albumin and is accumulated in the liver, where it is metabolized. The S stereoisomer is approximately 3 times (2.7 to 3.8) more potent than the R stereoisomer and it is metabolized mainly by the cytochrome P450 2C9. The R stereoisomer is metabolized by CYP1A2 and CYP3A4. [10]

Genetic factors modifying the dose-response relationship of warfarin are a) mutations 2C9*2 and 2C9*3 of the gene for the CYP2C9 enzyme leading to a disability to metabolize the S enantiomer, resulting in a prolonged elimination time, b) mutations in the Vitamin K oxide reductase gene, which is the target of Warfarin, resulting in the formation of enzymes with varying affinity to warfarin and c) mutations in the factor IX propeptide, leading to reduced levels of factor IX during treatment with the Vitamin K antagonist, which causes increased sensitivity and consequently increased bleeding.[10]

Interactions with other drugs may cause a change in the pharmacodynamics of warfarin. Drug interactions may reduce the absorption of warfarin (e.g., cholestyramine)[11], CYP2C9 enzyme induction thus increasing the clearance of warfarin[12] or stereoselective and nonselective enzyme inhibition which increases its antithrombotic effect[13]

1.2.3. Low Molecular Weight Heparin (LMWH)

Due to the multitude of LMWH that are available and the fact that they greatly vary in their pharmacologic profile, this section will take into consideration only enoxaparin, as it is the LMWH used as a comparator in the included studies of the present review.

Mechanism of action

Low molecular weight heparins disrupt the coagulation process as they bind to antithrombin (a serine protease inhibitor) through a pentassaccharide sequence. The interaction causes conformational change of the serine protease inhibitor, that amplifies the rate it inhibits activated factor Xa.[14]

Pharmacokinetics & Pharmacodynamics

Plasma anti-Xa and anti-IIa activity have been used to examine the pharmacokinetic profile of enoxaparin. Enoxaparin, after a subcutaneous injection, has an absolute bioavailability of almost 100%, and with increased dosages increases its maximum concentration (linear pharmacokinetics). The anti-Xa action of enoxaparin after a subcutaneous dose, is ten times higher than the anti-IIa activity. The volume of distribution is approximately 4 liters. It is mainly metabolized in the liver via desulfation and depolymerization and eliminated by the kidneys[15]. The t½ of enoxaparin varies between 5 and 7 hours, when administered as a single dose or continuously, respectively.[16] It has a mean molecular weight of about 4,500 daltons. A ratio of anti-Xa to anti-IIa of 3.6 has been estimated for enoxaparin in in vitro studies. Moreover, various other actions of enoxaparin have been detected[14–16] such as inhibition of factor VIIa, induction of endogenous Tissue Factor Pathway Inhibitor (TFPI) release and a reduction of von Willebrand factor (vWF) release into the circulation. When enoxaparin is administered in therapeutic doses the aPTT is increased by 1.5 to 2 times something not witnessed when prophylactic dosages are used.[16]

1.3. Perioperative Management

1.3.1. Dabigatran

General Management

Patients receiving dabigatran may have to temporary discontinue the medication before an elective procedure, the duration of discontinuation mainly depends on the bleeding risk of surgery and the renal function of the patient. In procedures/surgeries with minor bleeding risk dabigatran may have to be paused 12–24 h earlier before surgery.[17] In low bleeding risk surgery dabigatran has to be paused the day before surgery without bridging except in high thrombotic risk circumstances where bridging may be considered[17]. In high bleeding risk surgeries dabigatran has to be paused for at least two days preoperatively without bridging except in high thrombotic risk circumstances [17] Moreover, it should be noted that the period that dabigatran is paused is heavily influenced by the renal function of the patient. These recommendations are exhibited in figures 2 .

Regional anesthesia

In patients scheduled for regional anesthesia it is imperative to determine if the patient is schedule for a high bleeding risk (deep nerve/ neuraxial blocks) or a low bleeding risk (superficial neuraxial blocks) regional anesthesia[18]. Furthermore, it is crucial to determine the dosage of dabigatran the patient is receiving [high dosage: 110mg or 150mg BID / low dosage: 220 mg or 150 mg daily].

In patients on low dosage dabigatran, high bleeding risk regional anesthesia can be attempted at 48 hours of drug interruption without further testing, whereas low bleeding risk regional anesthesia can be attempted without interruption of dabigatran.[18]

On the other hand, in patients on high dosage dabigatran, high bleeding risk regional anesthesia can be attempted after at least 72 hours of drug interruption or until target laboratory values in patients with creatinine clearance <50 ml/min[18]. Target laboratory values are direct thrombin inhibitor (DTI) <30 ng/ml or a normal PT. Low bleeding risk anesthesia can be attempted without interruption[18].

If there is an neuraxial catheter in place then DOACs should not be administered until it is removed. If needed, a LMWH of low dosage can be administered.[18]

1.3.2. Warfarin

General management

The most recent guidelines pertaining the handling of warfarin in the elective perioperative setting are from the American College of Chest Physicians[19]

According to these guidelines warfarin must be discontinued 5 days or more before the surgery/ intervention and resumed with the usual dose within 24h after the surgery/intervention. In the case of an increased INR (greater than 1.5) 1 to 2 days before the surgery/intervention it is not suggested to routinely use Vitamin K. For patients taking vitamin K antagonists due to a mechanical heart valve, atrial fibrillation and for VTE the use of heparin bridging is not recommended except if these patients belong to a high thromboembolic risk category (table 3) where bridging is suggested. In patients with low to moderate thromboembolic risk it is not suggested to bridge warfarin with heparin. In patients requiring a dental, minor dermatologic or ophthalmologic, or a pacemaker or ICD implantation procedure it is suggested to continue VKA instead of interrupting it. In patients receiving VKA therapy who require discontinuation for a colonoscopy with anticipated polypectomy, heparin bridging is not suggested. If bridging warfarin with UFH then it is suggested to stop UFH for about four hours prior to surgery/intervention and to resume 24 hours post-surgery/intervention. For patients receiving LMWH as bridging, it is suggested to administer the final preoperative LMWH dose 24 hours prior to surgery/intervention and the first postoperative dose 24 hours after the intervention. Also, it is suggested to administer half the total daily dose of LMWH the day prior to the surgery instead of the full dose. Finally, it is not suggested to measure anti-factor Xa levels. Figure 3 displays graphically the perioperative management of warfarin.

Regional anesthesia

In patients receiving warfarin or any other vitamin – K antagonist (acenocoumarol, fluindione, phenprocoumon) high bleeding risk regional anesthesia should be attempted after INR has returned to normal values [18]. In patients scheduled for a low bleeding risk regional anesthesia, the VKAs may not be interrupted[18].

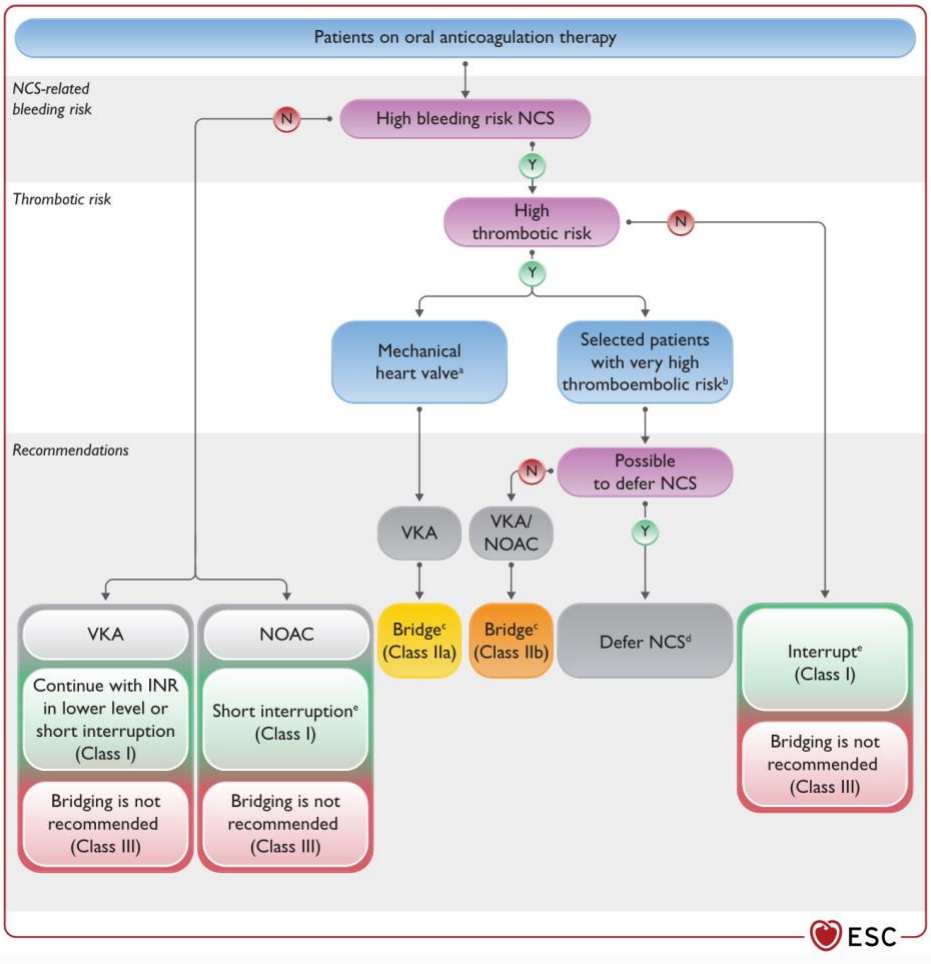


Figure 1. The general managent of patients receiving an oral anticoagulant before an elective surgery.[17]

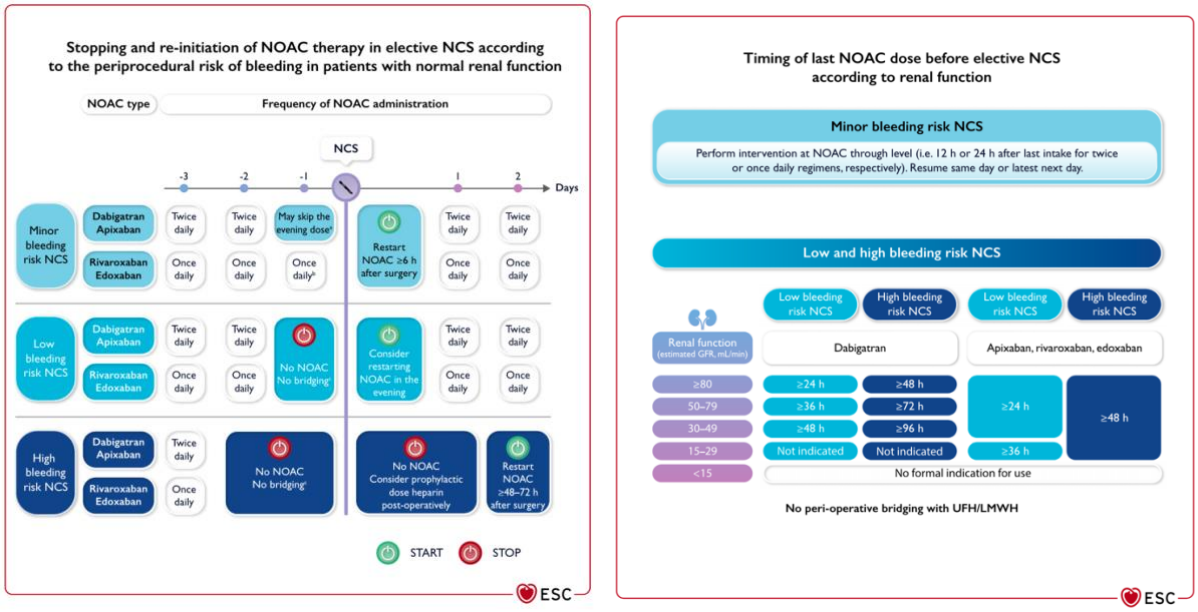
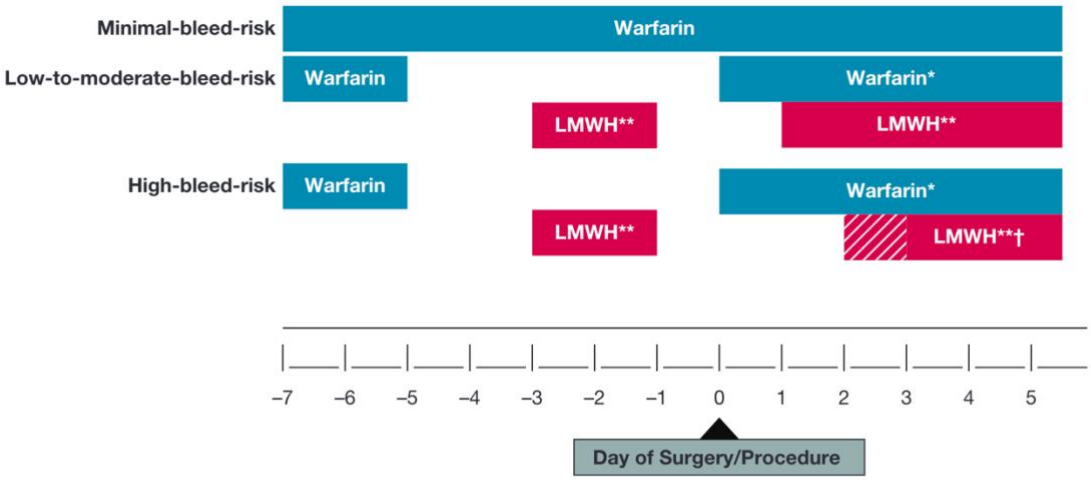


Figure 2 General management of direct oral anticoagulants before an elective non cardiac surgery[17]



Legend
*Warfarin can be resumed on the evening of procedure (D0) for most patients, or the day after procedure (i.e., D1) at the patient's usual maintenance dose.
**Bridging suggested for high thrombotic risk populations with full-dose, subcutaneous LMWH (e.g., enoxaparin, 1 mg/kg bid or 1.5 mg/kg daily or dalteparin, 100 IU/kg bid or 200 IU/kg daily), with the last dose given the AM of the day prior to the procedure (i.e., D-1) at half the total daily dose.
†Low-dose LMWH (e.g., enoxaparin, 40 mg daily or dalteparin 5,000 IU daily) can be used for VTE prophylaxis for first 24-72 hours post-procedure, with full dose LMWH resumed 2-3 days post-procedure.

Figure 3 General perioperative management of Warfarin[19]

1.3.3. Low Molecular Weight Heparin (LMWH)

General management & Regional anesthesia

There is no need to interrupt the LMWH dosing before a superficial nerve block. However, before a high bleeding risk intervention such as neuraxial or deep nerve block LMWH should be interrupted 12h if the dose is considered low (i.e. enoxaparin 40mg daily) or 24 hours if the dose is considered high. In the latter occasion if the creatinine clearance is less than 30ml/min the interruption must be for 48h or until target lab value (anti-Xa less than 0.1 IU/ml). High dose LMWH should not be administered with a catheter in situ.[18]

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	VTE
High (> 10%/year risk of arterial thromboembolism or > 10%/month risk of venous thromboembolism)	Mitral valve with major risk factors for stroke Caged ball or tilting-disc valve in mitral/aortic position Recent (< 3 month) stroke or TIA or other high risk stroke situations	CHA2DS2VASc score 7 or CHADS2 score of 5 or 6 Recent (< 3 month) stroke or TIA Rheumatic valvular heart disease	Recent (< 3 month and especially 1 month) VTE Severe thrombophilia Antiphospholipid antibodies Active cancer associated with high VTE risk
Moderate (4%-10%/year risk of arterial thromboembolism or 4%-10%/month risk of venous thromboembolism)	Bileaflet AVR with major risk factors for stroke	CHA2DS2VASc score of 5 or 6 or CHADS2 score of 3 or 4	VTE within past 3-12 month Recurrent VTE Non-severe thrombophilia Active cancer or recent history of cancer
Low (< 4%/year risk of ATE or < 2%/month risk of venous thromboembolism)	Bileaflet AVR without major risk factors for stroke	CHA2DS2VASc score of 1-4 or CHADS2 score of 0-2 (and no prior stroke or TIA)	VTE > 12 month ago

Table 3 Thromboembolic risk categories[19]

Knowledge up to now

Dabigatran in the perioperative setting is generally not interrupted for minor bleeding risk surgeries, whereas in low and high bleeding risk surgeries it is interrupted for 24 to 96 hours before the surgery.[17]

In three meta-analyses[20–22], dabigatran is shown to pose the same[20] or even lower[21,22] bleeding risk than warfarin. However, one was performed before 10 years[20], the other was performed only with studies on Japanese people[22] and the other one excluded randomized clinical trials with open label warfarin use[21]. Moreover, in four other meta-analysis[23–26] the administration of dabigatran as a prophylactic agent for venous thromboembolism was assessed. Bloom et al[23] demonstrated in their study that dabigatran had a lower incidence of major bleeding compared to VKA, however the study was conducted ten years ago and with a heterogenous population. Two studies of these studies[24,26], published in 2012 asserted that dabigatran had the same incidence of major bleeding with enoxaparin whereas the other[25] published in 2017 had the same results.

Based on the literature, dabigatran appears to be at least as safe as enoxaparin or warfarin in the perioperative period, however as new data emerge it is crucial that they are included in new systematic reviews such as this one.

Chapter 2 Methods

2.1. Review Aim

The goal of this review was to study and compare the bleeding risk in the perioperative or periprocedural setting of dabigatran versus non – DOACs, namely warfarin or low molecular weight heparin.

2.2. Search Strategy

We conducted a search in PubMed and Scopus, utilizing studies for January 2002 to March 2023. The search, in both databases, was conducted using keywords and Boolean terms (AND, OR). The key words that were used were the following: "postoperative", "preoperative", "intraoperative", "perioperative", "periprocedural", "dabigatran", "direct oral anticoagulant", "new oral anticoagulant", "anticoagulant", "bleeding", "bleeding risk" and "hemorrhage". The exact search query was the following: (preoperative OR intraoperative OR postoperative OR perioperative OR periprocedural) AND (direct oral anticoagulant OR new oral anticoagulant OR anticoagulant OR dabigatran) AND (bleeding OR bleeding risk OR haemorrhage). Moreover, reference lists for the included studies were used to search for relevant studies.

Studies that were included were randomized clinical trials, comparing dabigatran (not combined with other antithrombotic or antiplatelet medication) with non-direct oral anticoagulants in the perioperative period.

Studies that belong to a following category were excluded: Meta-Analysis, Systematic Review, Case control studies, Case Series/Case Reports, Observational Studies, Expert opinions, Editorials, Letter to the editors, Narrative Reviews, unpublished manuscripts, conference reports, non-Human studies, non-English language, irrelevant title, irrelevant abstract, irrelevant full text. Moreover, studies were excluded if the outcome of interest was not measured. The original study investigators were not contacted to confirm or obtain relevant information.

The PICO elements of this study, as well as the search strategy and exclusion criteria are depicted, in table 4.

Table 4 The PICO elements of this study.

PICO Elements	P (Patients, participants, population)	I (intervention)	I (intervention)	O (Outcome)	Time
Keywords	Perioperative patients	On Dabigatran	Patients not on DOAC	Bleeding Risk	2002-2023
Search strategy	Perioperative OR Periprocedural OR Preoperative OR Postoperative OR Intraoperative	Dabigatran OR Direct Oral Anticoagulant OR New Oral Anticoagulant OR Anticoagulant		Bleeding OR Bleeding Risk OR Hemorrhage	
Exclusion criteria	Meta-Analysis, Systematic Review, Case control studies, Case Series/Case Reports, Observational Studies, Expert opinions, Editorials, Letter to the editors, Narrative Reviews, unpublished manuscripts, conference reports, non-Human studies, non-English language, irrelevant title, irrelevant abstract, irrelevant full text				
Search	Databases (PubMed and Scopus) References cited in study reports included in the systematic review.				

2.3. Data extraction and assessment of the studies quality.

The data extraction was conducted using a data extraction table. The data that were extracted were the total population enrolled in the study, the population randomized and the population used for the assessment of bleeding. Moreover, the population's age, weight, gender and creatinine clearance were collected. Furthermore, the study design, the period of study, the type of surgery and the population that belonged to each subgroup of drug dosage and the number of bleeding events major, clinically relevant or minor were collected. Data that were expressed as percentages were transformed to absolute numbers by multiplying the percentage with the total number of the relevant variable.

The quality assessment was conducted using the second edition of the Risk of Bias assessment tool of COCHRANE by one reviewer. The domains assessed by this tool are randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Moreover, an overall risk of bias judgement that summarised across domains/components/items was made, grading as low

risk of bias if judged to be at low risk for all domains, graded as some concerns if in at least one domain is judged as some concerns, and graded as high risk if it is judged as high risk in at least one domain or the study is judged to have some concerns for multiple domains.

The quality assessment and data extraction were performed by one person, A.A.M.

2.4. Definitions

Major bleeding, Clinically significant bleeding and Minor bleeding was defined according to published guidelines (Table 5)[27,28].

Table 5. Bleeding Definitions

Major Bleeding	Clinically relevant bleeding	Minor Bleeding Events
Fatal bleeding	spontaneous skin hematoma ‡ 25 cm2	Everything else
Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome	wound hematoma ‡ 100 cm2	
Extrasurgical site bleeding causing a fall in hemoglobin level of 20g/L or more, or leading to transfusion of two or more units of whole blood or red cells	epistaxis > 5 min	
Surgical site bleeding that requires a second intervention or a hemarthrosis of sufficient size as to interfere with rehabilitation, resulting in prolonged hospitalization or a deep wound infection	spontaneous macroscopic hematuria or that lasting > 24 h if associated with an intervention	
Surgical site bleeding that is unexpected and prolonged and/ or sufficiently large to cause hemodynamic instability. There should be an associate fall in hemoglobin level of at least 20 g/L or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding.	spontaneous rectal bleeding, gingival bleeding > 5 min, and any other bleeding event judged as clinically significant by the investigator	

2.5. Statistical Analysis

As this is a qualitative synthesis, no statistical analysis was performed. All the mentioned p values, standard errors or 95% confidence intervals are taken from the respective studies. If none are mentioned, then they are also not mentioned in the respective studies.

Chapter 3 Results

3.1. Study Selection

In total 2510 studies were found. From these, 347 were deleted due to being duplicates, 2149 were excluded for having an irrelevant title or abstract, 14 were sought and found for full text and 6 were exclude, one because there was not control drug[29], another because dabigatran was not included in the studied drugs[30], three were sub-studies[31–33] of other included studies and thus containing same sub-populations, in one[34] because dabigatran was received in combination with other anti-platelet drugs and in one because the way the groups were created did not facilitate the comparison between drugs[35]. Moreover, from the search in the reference list of the included studies two more studies were found, sought and retrieved and added in our study. To summarize, 9 studies[36–44] are included in this systematic review. The PRISMA flow chart is depicted in figure 4.

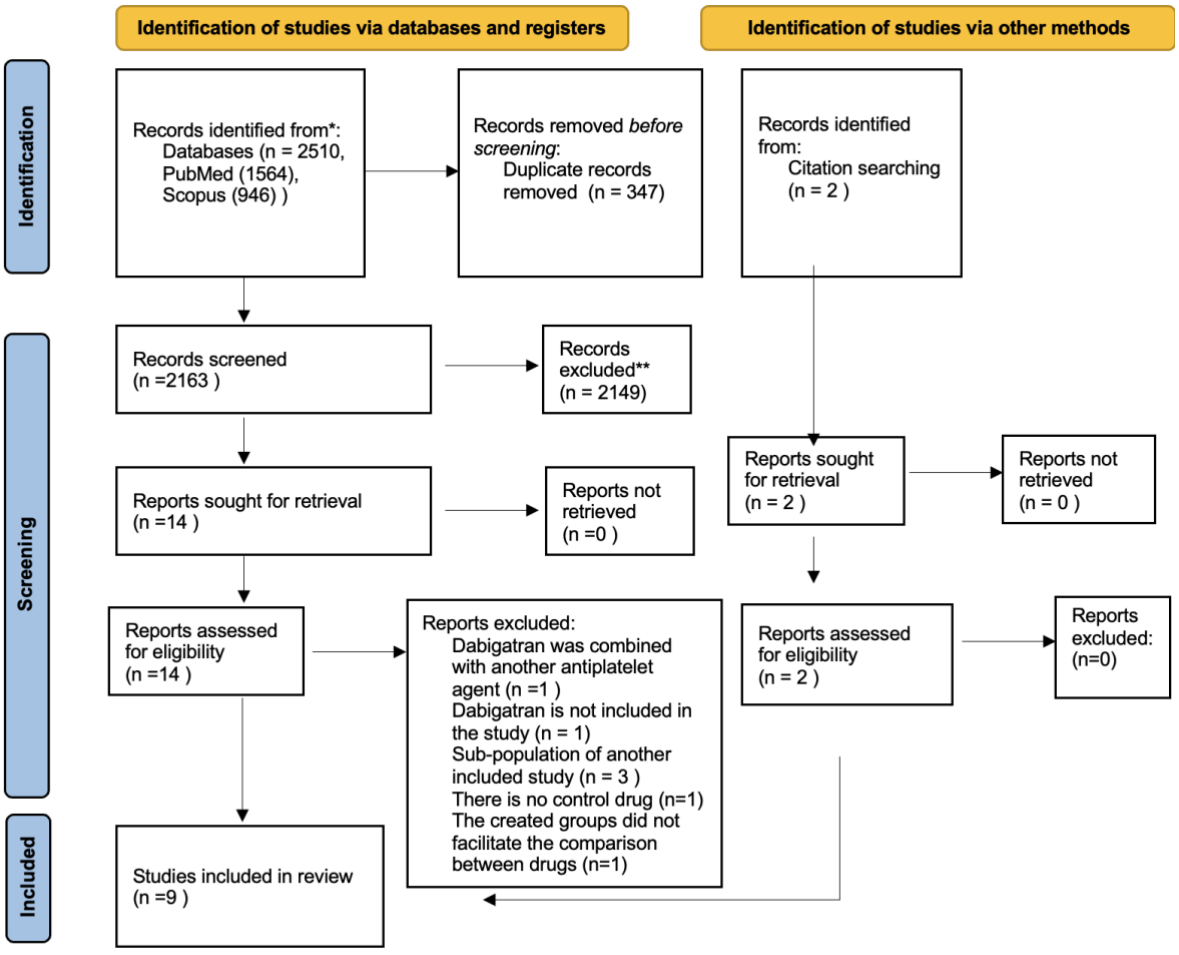


Figure 4 The PRISMA flow chart

From these 9 studies, five[40–44] studied the prophylactic administration of dabigatran in different dosages for the prevention of venous thromboembolism after total hip replacement[40,43], total knee replacement[41,44] or both surgeries[42]; three[36–38] studied the administration of dabigatran in the periprocedural period of ablation in patients with atrial fibrillation and one[39] the administration of dabigatran during the perioperative period of various surgeries compared to warfarin.

3.2. Patient Selection

Baseline patient characteristics, the total population of each drug group and of each sub-population based on different drug dosages, are depicted on tables 6,7 and 8.

In all included studies[35–44] there was no difference between the groups, and the sub-groups, in baseline characteristics, namely weight, age and creatinine clearance. All the participants had a creatinine clearance above 60 ml/min and did not belong in any extreme weight or age category.

Study 1

In this randomized double-blind study by Eriksson et al.[42], in 1949 patients, 61% of the population being female, undergoing total hip or knee replacement various dabigatran doses were studied as postoperative prophylaxis for venous thromboembolism, namely 50 mg, 150 mg and 225 mg twice daily, and 300 mg once daily all of which were started 1-4 h postoperatively or as soon as possible and compared with 40 mg of enoxaparin, given in the evening before surgery or postoperatively based on differing regional guidelines. The primary efficacy outcome was the incidence of VTE during the treatment period which was 6-10 days postoperatively until mandatory bilateral venography was performed. The primary safety outcome was major bleeding during the treatment period.

Study 2

In this a randomized, double-blind study by Eriksson et al[43], in 3463 patients, 56% of the population being female, undergoing total hip replacement two different doses of dabigatran, once daily 220mg or 150mg, were tested as postoperative prophylaxis for venous

thromboembolism and were compared with enoxaparin 40mg subcutaneously once daily. The first dabigatran dose was halved and given one to four hours postoperatively, provided there was sufficient hemostasis. If dabigatran was administered on the day after surgery, two full doses were given with a gap of at least 12 hours. Enoxaparin was given in the evening before surgery or postoperatively based on differing regional guidelines. The primary efficacy outcome was venous thromboembolism episodes and all-cause mortality during treatment, which lasted for 28-35 days until venography. The primary safety outcome was the occurrence of bleeding events (major, clinically relevant or minor bleeding) during the treatment period.

Study 3

In this randomized double-blind study by Eriksson et al[41], 2076 patients, 65% of the population being female, undergoing total knee replacement were randomized to receive dabigatran, once daily 220 mg or 150mg, as postoperative prophylaxis for venous thromboembolism and were compared with patients receiving subcutaneously enoxaparin 40mg once daily. The first dabigatran dose was halved and given one to four hours postoperatively, provided there was sufficient hemostasis. If dabigatran was administered on the day after surgery, two full doses were given with a gap of at least 12 hours. Enoxaparin was given in the evening before surgery or postoperatively based on differing regional guidelines. The primary efficacy outcome was venous thromboembolism episodes and all-cause mortality during treatment, which lasted for 6-10 days until mandatory bilateral venography. The primary safety outcome was the occurrence of bleeding events (major, clinically relevant or minor bleeding) during the treatment period.

Study 4

In this randomized, double-blind Ginsberg et al[44], 2596 patients, 58% of the population being female, undergoing primary elective unilateral total knee arthroplasty were randomized to three groups, two groups of dabigatran, 220mg and 150 mg once daily, and one group of enoxaparin, 30 mg subcutaneously twice a day, as postoperative venous thromboembolism prophylaxis. The first dose of dabigatran was halved and was administered six to twelve hours after the surgery, provided the hemostasis was adequate. If dabigatran was not administered the day of surgery, a full dose was administered as the first dose the morning after surgery. The first subcutaneous injection was given twelve to twenty-four hours after surgery, usually the

next morning. The duration of treatment was twelve to fifteen days, followed by mandatory bilateral venography, within twelve hours of the last administration of medication. The primary efficacy outcome was venous thromboembolism episodes and all-cause mortality during treatment. The primary safety outcome was the occurrence of bleeding events (major, clinically relevant or minor bleeding) during the treatment period.

Study 5

In this randomized, double-blind trial Eriksson et al[40], 2013 patients, 52% of the population being female, undergoing primary total hip replacement were randomized to receive dabigatran 220 mg once daily or a subcutaneous dose of enoxaparin 40 mg, as prophylaxis for postoperative venous thromboembolism. The first dabigatran dose was halved and given one to four hours postoperatively, provided there was sufficient hemostasis. If dabigatran was not administered the day of surgery, a full dose was given the next morning. Enoxaparin was given in the evening before surgery or postoperatively based on differing regional guidelines. The primary efficacy outcome was venous thromboembolism episodes and all-cause mortality during treatment, which lasted for 28-35 days until mandatory bilateral venography. The primary safety outcome was the occurrence of major bleeding events during the treatment period.

Study 6

In a sub-study of the RE-LY trial[45], a randomized, with open label use of warfarin and blinded use of different dabigatran doses, non-inferiority trial, Healey et al[39], assessed the perioperative bleeding in 4591 patients, 32% of the population being female, with atrial fibrillation, receiving dabigatran, 110 mg or 150 mg twice daily, or warfarin. In this study, two regiments of dabigatran interruption were followed, in the first regiment dabigatran was interrupted for 24 hours for all procedures whereas in the second, due to an improved understanding of the pharmacologic principles of dabigatran, in low bleeding risk surgeries dabigatran was interrupted for 24 hours and in high bleeding risk surgeries for 2-5 days. In this study the perioperative period was defined as 7 days before the procedure and 30 days after. The efficacy outcome was thromboembolic events, both venous and arterial, and death, and the safety outcome was major bleeding both during the perioperative period.

Study 7

In this randomized, non-blinded, single center study by Nin et al[38], 90 patients, 18% of the population being female, scheduled to undergo ablation for atrial fibrillation were randomized to receive dabigatran 110 mg twice daily or warfarin. Both drugs, dabigatran and warfarin were withheld the morning of the procedure. The outcome of interest in this study was bleeding from any source, observed within 48 hours after the ablation procedure, requiring neither a transfusion nor surgery, but only medical attention.

Study 8

In this randomized, open-label trial by Calkins et al[37], 635 patients, 25% of the population being female, scheduled to undergo ablation for atrial fibrillation were randomized to receive dabigatran, 150 mg twice daily, or warfarin. Ablation was performed after the patients had received 4 to 8 weeks of uninterrupted anticoagulation. Coagulation was not interrupted for the procedure and was continued for 8 weeks after the procedure. The primary end point was the incidence of major bleeding events from the first femoral puncture and up to 8 weeks after ablation.

Table 6 Baseline characteristics of the included studies.

Source	Study Design	Study Population	Outcome	Study period	Surgery/Procedure	Interv. Drug	Control Drug
Eriksson et al. '05	RCT	1949	Major bleeding	6-10 days	THR/TKR	Dabigatran	Enoxaparin
Eriksson et al. '07 (Lancet)	RCT	3463	Bleeding events	28-35 days	THR	Dabigatran	Enoxaparin
Eriksson et al. '07 (JTH)	RCT	2076	Bleeding events	6-10 days	TKR	Dabigatran	Enoxaparin
Ginsberg et al. '09	RCT	2596	Bleeding events	12-15 days	TKR	Dabigatran	Enoxaparin
Eriksson et al. '11	RCT	2013	Major bleeding	28-35 days	THR	Dabigatran	Enoxaparin
Healey et al. '12	RCT	4591	Bleeding events	7 days preop. and 30 days postop.	Various surgeries and procedures	Dabigatran	Warfarin
Nin et al. '13	RCT	90	Minor bleeding	2 days	Ablation	Dabigatran	Warfarin
Calkins et al. '17	RCT	635	Bleeding events	8 weeks postop	Ablation	Dabigatran	Warfarin
Nogami et al. '19	RCT	442	Major bleeding	3 months postop	Ablation	Dabigatran	Warfarin

Abbreviations: RCT: randomised clinical trial, THR: total hip replacement, TKR: total knee replacement, JTH: Journal of Thrombosis and Hemostasis, preop: preoperative, postop: postoperative

Study 9

Finally, in this randomized trial by Nogami et al[36], 442 patients, 25% of the population being female, scheduled to undergo ablation for atrial fibrillation were randomized to receive dabigatran, 150 mg or 110 mg twice daily based on the dose reduction criteria in the package inert, or warfarin. Both drugs were administered for at least 4 weeks. Before the procedure, one or two dabigatran doses were withheld according to the treating physician discretion, whereas warfarin was continued. The primary end points were the incidence of perioperative embolism and the formation of thrombus in the preablation period. The outcome of interest, the incidence of major bleeding events, was assessed from the initiation of the procedure until 3 months post ablation.

Table 7 Baseline characteristics of patients receiving Dabigatran (intervention drug)

Source	Interv. Drug	Interv. Drug Population (female/total)	Interv. Drug Age	Interv. Drug Patient weight	Interv. Drug Patient Cr.Cl. (ml/min)
Eriksson et al. '05	Dabigatran • 50 mg bid • 150 mg bid • 300 mg qd • 225 mg bid	950/1557 • 223/389 • 252/390 • 246/385 • 229/225	65.9 (20–93) • 66.1 (31–88) • 65.9 (34–89) • 66.5 (21–88) • 65.9 (33–93)	79 (43–130) • 79 (46–125) • 79 (44–130) • 79 (43–128) • 79 (44–130)	Not Stated
Eriksson et al. '07 (Lancet)	Dabigatran • 220 mg qd • 150 mg qd	1303/2309 • 636/1146 • 667/1163	Not Stated • 65 ±10 • 63 ±11	Not Stated • 79 ±15 • 79 ±15	Not Stated • 89 ±29 • 90 ±31
Eriksson et al. '07 (JTH)	Dabigatran • 220 mg qd • 150 mg qd	892/1382 • 441/679 • 451/703	Not Stated • 67 ±9 • 68 ±9	Not Stated • 82 ±15 • 83 ±15	Not Stated
Ginsberg et al. '09	Dabigatran • 220 mg qd • 150 mg qd	993/1728 • 486/857 • 507/871	Not Stated • 66.2 ±9.5 • 65.9 ±9.5	Not Stated • 88.4 ±19.1 • 87.6 ±20.0	Not Stated • 83.6 ±30.1 • 82.3 ±30.0
Eriksson et al. '11	Dabigatran • 220 mg qd	541/1010	62 ± 12	79 ± 17	97 ± 34
Healey et al. '12	Dabigatran • 110 mg bid • 150 mg bid	965/3033 • 448/1487 • 517/1546	Not Stated • 72.3 ±7.7 • 72.5 ±7.7	Not Stated • 29.6 ±6 (BMI) • 29.3 ±5.7 (BMI)	Not Stated • 71.9 ±35.0 • 69.9 ±35.7
Nin et al. '13	Dabigatran • 110 mg bid	7/45	61 ± 11	69.6 ± 14.5	64.1 ± 13.1
Calkins et al. '17	Dabigatran • 150 mg bid	87/317	59.1±10.4	28.5 (BMI)	Not stated

Nogami et al. '19	Dabigatran • 110 mg bid or 150 mg bid	49/220	65.0 (59.0-71.0)	66.9 (59.7-75.0)	80.1 (65.4-94.1)

Abbreviations: Inter.: intervention, Cr. Cl.: Creatine Clearance, Clinically Rel.: clinically relevant

Table 8 Baseline Characteristics of patients receiving Warfarin or Enoxaparin.

Source	Control Drug	Control Drug Population (female/total)	Control Drug Population Age	Control Drug Patient weight	Control Drug Patient CrCl (ml.min)
Eriksson et al. '05	Enoxaparin 40mg sc qd	241/392	65.0 (20–86)	79 (47–125)	Not Stated
Eriksson et al. '07 (Lancet)	Enoxaparin 40mg sc qd	651/1154	64 (11)	78 (15)	89 (30)
Eriksson et al. '07 (JTH)	Enoxaparin 40mg sc qd	478/694	68 ± 9	82 ± 15	Not Stated
Ginsberg et al. '09	Enoxaparin 30mg sc bid	504/868	66.3 ± 9.6	88.0 ± 19.2	82.9 (29.5)
Eriksson et al. '11	Enoxaparin 40mg sc qd	501/1003	62 ± 11	80 ± 17	97 ± 32
Healey et al. '12	Warfarin	496/1558	72.6±7.4	29.2 ±5.8 (BMI)	69.8 (33.7)
Nin et al. '13	Warfarin	9/45	61 ± 6	67.0 ± 9.8	63.2 ± 12.0
Calkins et al. '17	Warfarin	73/318	59.3±10.3	28.8 (BMI)	Not Stated
Nogami et al. '19	Warfarin	62/222	66.0 (59.0-71.0)	66.2 (59.7-73.0)	77.8 (64.6-97.2)

Abbreviations: Cr. Cl.: Creatine Clearance, Clinically Rel.: clinically relevant

3.3 Bleeding Risk of Dabigatran

The incidents of bleeding per study are summarized in table 9.

Study 1

In the study by Eriksson et al[42], there were 16 incidents of major bleeding in 390 (4.1%) subjects in the 150 mg bid group, 18 in 385 (4.6%) in the 300 mg qd group, 15 in 225 (6.6%) in the 225 mg bid and 1 in 389 (0.25%) in the 50 mg bid respectively. Moreover, when compared to the incidence of major bleeding in the 40mg qd enoxaparin group, 8 incidents in 392 patients, it was reduced in the 50 mg group (0.3% vs. 2.0%, P = 0.047), and insignificant in the 150 mg bid (4.1%, p= 0.1), 225 mg bid (3.8%, p= 0.15) and 300 mg qd (4.7%, P = 0.051) groups.

Study 2

In the study by Eriksson et al[43] there were 23 incidents of major bleeding in 1146 (2%) patients receiving 220 mg qd, 15 in 1163 (1.2%) patients receiving 150 mg qd of dabigatran , and 18 in 1154 (1.5%) patients receiving enoxaparin 40 mg sc qd. There was no significant difference in major bleeding events between both dabigatran doses and enoxaparin (p=0.44 for 220 mg and p=0.60 for 150 mg, respectively).

Study 3

In the study by Eriksson et al[41], there were 10 incidents of major bleeding in 679 (1.5%) patients receiving 220 mg qd dabigatran, 9 in 703 (1.3%) patients receiving 150 mg qd dabigatran and 9 in 694 (1.3%) patients receiving enoxaparin 40 mg sc qd. There was insignificant difference for major bleeding between dabigatran and enoxaparin (P = 0.82 for 220 mg and P =1.0 for 150 mg, respectively).

Study 4

In the study by Ginsberg et al[44], 5 out 857 (0.6%) patients receiving 220 mg qd dabigatran, 5 out of 871 (0.6%) patients receiving 150 mg qd dabigatran and 12 out of 868 (1.4%) patients receiving enoxaparin 30mg sc bid experienced a major bleeding event. There was no significant difference between the three groups.

Study 5

In the study by Eriksson et al[40], 14 patients out of 1010 (1.4%) experienced major bleeding in the dabigatran group and nine out of 1003 (0.9%) in the enoxaparin group. There was no statistically significant difference between the two groups in bleeding events (p=0.40).

Study 6

In the study by Healey et al[39], 57 out of 1487 (3.8%) and 78 out of 1546 (5.1%) patients receiving dabigatran 110 mg bid and 150 mg bid respectively experienced a major bleeding event whereas 72 out of 1558 (4.6%) patients receiving warfarin had a similar episode. There was no statistically significant difference between those groups [Dabigatran 110 mg vs

Warfarin, 1.03 (95% CI: 0.81–1.31, p=0.81) and Dabigatran 150mg vs Warfarin 1.15 (95% CI: 0.91–1.45, p=0.24)], nor there was in the groups before and after the amendment of the interruption period (dabigatran 110 mg BID versus warfarin, (p=0.81), and for dabigatran 150 mg BID versus warfarin, (p=0.81)].

Study 7

In the study by Nin et al[38], 9 out of 45 (20%) patients receiving dabigatran 110 mg bid experienced a minor bleeding event, whereas 20 out of 45 (44%) patients receiving warfarin had a similar episode. There was a significant difference between the two groups (20% vs 44%; P = 0.013).

Study 8

In the study by Calkins et al[37], 5 out of 315 (1.6%) patients in the dabigatran 150 mg bid group experienced a major bleeding event whereas 22 out of 318 (6.9%) patients in the warfarin group had a similar event, which was a statistically significant difference ([1.6%] vs. [6.9%]; absolute risk difference, –5.3 percentage points; 95% confidence interval [CI], –8.4 to –2.2; P<0.001).

Study 9

In the study by Nogami et al[36], 3 out of 220 (1.4%) participants in the dabigatran (150mg and 110mg bid) group had a major bleeding event, whereas in the warfarin group 11 out of 222 (5%) had a similar event. There was a statistically significant difference between these groups (RR= 0.273 [95% CI, 0.076-0.980] p=0.03)

Table 9. Bleeding incidents in patients receiving Dabigatran or Enoxaparin/ Warfarin.

Source	Dabigatran				Enoxaparin/ Warfarin			
	Drug dose group	**Combined Bleeding**	**Major Bleeding**	**Clinically Rel. and Minor Bleeding**	**Control drug Group**	**Combined Bleeding**	**Major Bleeding**	**Clinically Rel. and Minor Bleeding**
Eriksson et al. '05	• 50 mg bid • 150 mg bid • 300 mg qd • 225 mg bid	• 28 • 63 • 74 • 73	• 1 • 16 • 18 • 15	• 27 • 47 • 56 • 58	Enoxaparin 40mg sc qd	43	8	35
Eriksson et al. '07 (Lancet)	• 220 mg qd • 150 mg qd	• 141 • 142	• 23 • 15	• 118 • 127	Enoxaparin 40mg sc qd	132	18	114
Eriksson et al. '07 (JTH)	• 220 mg qd • 150 mg qd	• 110 • 116	• 10 • 9	• 100 • 107	Enoxaparin 40mg sc qd	115	9	106
Ginsberg et al. '09	• 220 mg qd • 150 mg qd	• 28 • 27	• 5 • 5	• 23 • 22	Enoxaparin 30mg sc bid	33	12	21
Eriksson et al. '11	220 mg qd	98	14	84	Enoxaparin 40mg sc qd	83	9	74
Healey et al. '12	• 110 mg bid • 150 mg bid	• 177 • 217	• 57 • 78	• 169 • 193	Warfarin	194	72	122
Nin et al. '13	110 mg bid	9	Not Studied	9	Warfarin	20	0	20
Calkins et al. '17	150 mg bid	64	5	59	Warfarin	76	22	54
Nogami et al. '19	110 mg bid or 150 mg bid	3	3	Not Stated	Warfarin	11	11	Not stated

3.4 Risk of Bias Assessment

Risk of bias was assessed using the Risk of Bias assessment tool by Cochrane. The results are depicted in figures 5 and 6.

Study 1

The study by Eriksson et al[42] was considered a) as low risk in the randomization process, as the allocation was computer generated and was performed the day before surgery, after the patietnts were enrolled and the baseline characteristics between patient groups were the same, b) as low risk in deviation from the intended intervention as it was a double blind trial with an intention-to-treat analysis, c) as low risk in missing outcome data as only 24 out of 1973

patients were not treated, d) as low risk in the measurement of the outcome as it was assesed based on guidelines and classified by a centralized independent committee, the same method of measurement was applied to all groups and the study is double blinded and e) in the selection of the reported results there were some concerns as there was no access to the pre publish design of the study. Overall, the study was characterized as some concerns by the algorithm and as low risk by the investigator as there were no hints of bias arising from selective reporting.

Study 2

Another study by Eriksson et al[43] was considered a) as low risk in the randomization process, as the allocation was computer generated and was performed the day before surgery, after the patietnts were enrolled and the baseline characteristics between patient groups were the same, b) as low risk in deviation from the intended intervention as it was a double blind trial with an intention-to-treat analysis, c) as low risk in missing outcome data as based on the power analysis, 720 patients per group were sufficient. In this study, each group has more than 720 patients (1163,1154,1146), d) as low risk in the measurement of the outcome as it was assesed based on guidelines and classified by a centralized independent committee, the same method of measurement was applied to all groups and the study is double blinded and e) in the selection of the reported results there were some concerns as there was no access to the pre publish design of the study. Overall, the study was characterized as some concerns by the algorithm and as low risk by the investigator as there were no hints of bias arising from selective reporting.

Study 3

This study by Eriksson et al[42] was considered a) as low risk in the randomization process, as the allocation was computer generated and was performed the day before surgery, after the patietnts were enrolled and the baseline characteristics between patient groups were the same, b) as low risk in deviation from the intended intervention as it was a double blind trial with an intention-to-treat analysis, c) as low risk in missing outcome data as based on power analysis, 500 patients were required in each group and in the study each group had >500 patients, d) as low risk in the measurement of the outcome as it was assesed based on guidelines and classified by a centralized independent committee, the same method of measurement was applied to all

groups and the study is double blinded and e) as low risk in the selection of the reported results as the analysis and outcome report was conducted according to the study desgin published in clinicaltrials.gov. Overall, the study was characterized as low risk by the algorithm and by the investigator.

Study 4

This study by Ginsberg et al[44] was considered a) as low risk in the randomization process as the allocation was randomized based on an interactive response voice system,the study was double blinded and patient baseline characteristics were the same between the three groups., b) as low risk in deviation from the intended intervention as it was a double blind trial with an intention-to-treat analysis, c) as low risk in missing outcome data as based on power analysis, 650 patients were required in each group. In this study each group has >650 patients, d) as low risk in the measurement of the outcome as Bleeding events were measured based on accepted published guidelines and classified aby an independent expert committee, The same methods were applied between groups and the commitee was independent and e) in the selection of the reported results there were some concerns as there was no access to the pre publish design of the study. Overall, the study was characterized as some concerns by the algorithm and as low risk by the investigator as there were no hints of bias arising from selective reporting.

Study 5

This study by Eriksson et al[40] was considered a) as low risk in the randomization process, as the allocation was computer generated and was performed the day before surgery, after the patietnts were enrolled and the baseline characteristics between patient groups were the same, b) as low risk in deviation from the intended intervention as it was a double blind trial with an intention-to-treat analysis, c) as low risk in missing outcome data as based on the power analysis, as each group had a higher number of participants than the one prespecified by the power analysis, d) as low risk in the measurement of the outcome as it was assesed based on guidelines and classified by a centralized independent committee, the same method of measurement was applied to all groups and the study is double blinded and e) in the selection of the reported results there were some concerns as there was no access to the pre publish design of the study. Overall, the study was characterized as some concerns by the algorithm

and as low risk by the investigator as there were no hints of bias arising from selective reporting.

Study 6

The study by Healey et al[39], was considered as a) low risk in the randomization process as the randomization was performed by a computer, and the baseline characteristics were not different, b) as low risk in deviation from the intended intervention as the study drug was administered in a blinded fashion, the people who assessed the outcomes were blinded to the intervention received, no deviations were mentioned, and with an intention-to-treat analysis, c) as low risk in missing outcome data, as data were available for all randomized patients, d) as low risk in measurement of the outcome even though it was conducted through questionnaires, several precautionary steps were taken in order to mitigate the risk, and e) as low risk in selection of the reported result as the data reported were analyzed based on a prespecified data analysis plan. Overall, the study was charectirized by the algorithm and the investigator as low risk.

Study 7

The study by Nin et al[38] was considered as a) low risk in the randomization process as it was randomized by using blocks, so the last person allocated was known, b) as low risk in deviation from the intended intervention as even though the study was not blinded, there were no mentioned deviations due to trial context with an intention-to-treat analysis, c) as low risk in the missing outcome data as all patients randomized were treated, d) as low risk in measurement of the outcome, even though the measurement method in not detailed it was performed in the same basis between groups, and e) as some concerns in selection of the reported result as there is no pre-publish study design. Overall, the study was deemed as some concerns by the algorithm and the investigator due to some concerns in selection of the reported result.

Study 8

The study by Calkins et al[37] was considred as a) low risk in the randomization process, even though it is not mentioned in detail it is assumed due to the experience of the investigators and the baseline characteristics between patient groups were the same, b) as low risk in deviations from the intended intervention even though it was open label, there were no mentions of deviations and with an intention-to-treat analysis, c) as low risk in the missing outcome data as for the treated set nearly all patients randomized had available data, d) as low risk in measurement of the outcome, as it was based on published guidelines, the same methods were applied to all groups and it was assessed by an independent blinded committee and e) as low risk in the selection of the reported result, even though there was no access to a pre-publish study design it was assumed that there was no selective reporting due to the experience of the investigators. Overall, the study was deemed to be as low risk by the algorithm and the investigator.

Study 9

Finally the study by Nogami et al[36] was considered as a) low risk in the randomization process as it was a computer generated allocation sequence and there were no differences between the groups, b) as low risk in deviations from intended intervention as even though it was an open label study there were no mentioned deviations and with an intention-to-treat analysis, c) as low risk in the missing outcome data as there were available data for nealy all patients required based on the conducted power analysis, d) as low risk in the measurement of the outcome as it was performed based on published guidelines, the same methods were applied to all groups, and the outcome assessors were blinded and independent and e) as low risk in selection of the reported result as it was performed based on a pre-publish study design. Overall, the study is deemed as low risk by the algorithm and the investigator.

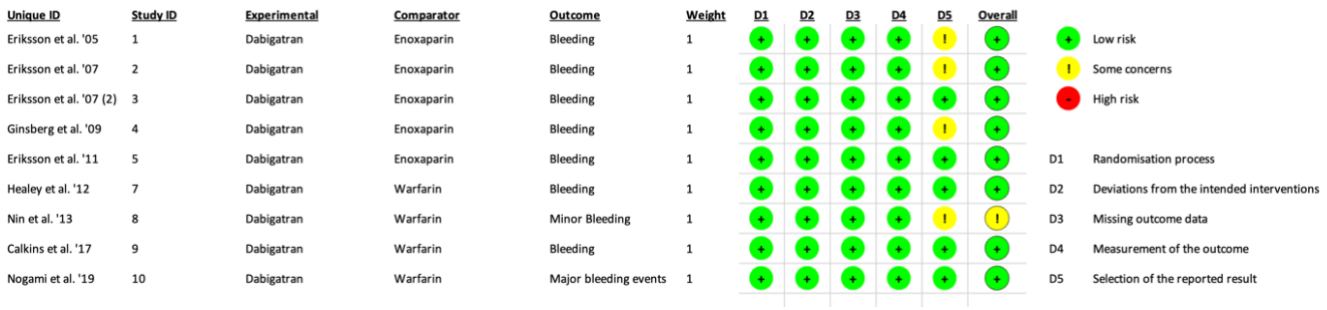


Figure 4 Risk of bias assessment

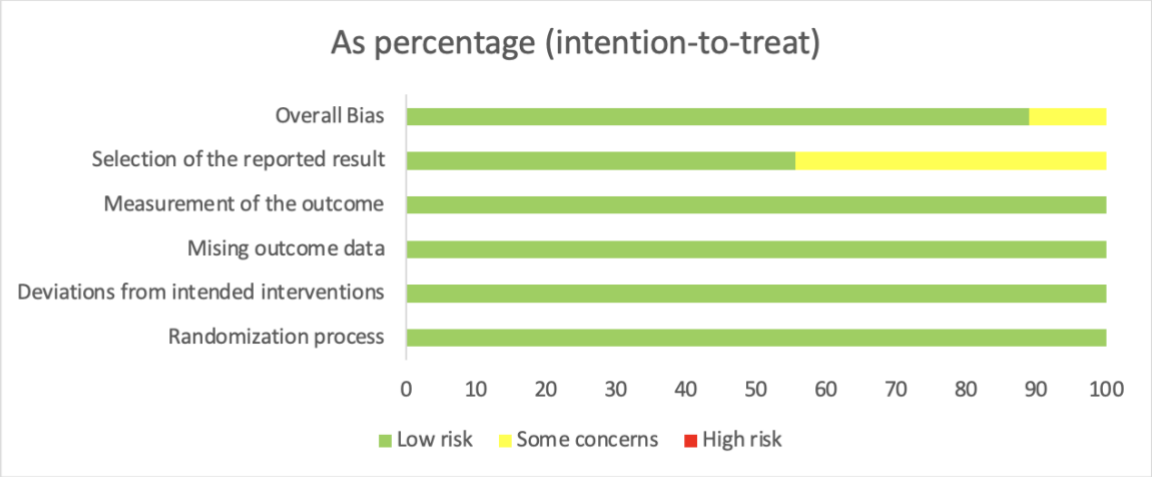


Figure 6 Risk of bias, expressed as percentages.

Chapter 4. Discussion

The purpose of this review was to evaluate the bleeding risk of dabigatran in the perioperative setting compared to low molecular weight heparins and warfarin.

Nine studies[36–44] were included in this systematic review among which 5 [40–44] comparing the use of dabigatran versus enoxaparin as a prophylactic agent against venous thromboembolism following hip or knee total replacement surgery and 4 studies[36–39] comparing the administration of dabigatran versus warfarin in the periprocedural period of patients with atrial fibrillation scheduled to undergo ablation. The overall risk of bias of the study is deemed low, as 8 out of 9 studies are deemed as low risk of bias and one as some concerns for the risk of bias.

Bleeding risk of patients receiving dabigatran for postoperative VTE prophylaxis.

In 4 out of 5 studies[40,41,43,44], with a total of 10148 patients, comparing dabigatran (150 mg and 220 mg qd) with enoxaparin (40 mg sc qd or 30mg sc bid) for prevention of VTE, in patient receiving total hip or knee replacement, the major bleeding events between these two groups were the same. In the other study[42], with 1949 patients undergoing total hip or knee replacement, even though the majority of the dabigatran dosages used were much higher than those in clinical practice nowadays there was still no significant increased incidence of major bleeding when compared to the enoxaparin group. These studies were randomized clinical trials, with a low risk of bias, examining the administration of dabigatran as a prophylactic agent for VTE following hip or knee replacement surgery. Based on the above results, dabigatran is non-inferior to enoxaparin as postoperative VTE prevention in patients undergoing hip or knee surgery.

Our results are comparable with those from previous studies[26,46,47], comparing DOACS with LMWH for post-operative VTE prevention. In a study by Outes et al[26], with a population of 38747 patients undergoing total knee or hip replacement, DOCS were compared with enoxaparin as postoperative VTE prophylaxis. Dabigatran exhibited a non-inferior profile compared to enoxaparin in major bleeding incidence. In the study by Marcucci[46] et al, involving 45455 patients undergoing non-cardiac surgery, DOACs were compared with LMWH as VTE prophylaxis. Dabigatran (with a dose of 220mg once daily), exhibited a non-inferior profile in major bleeding occurrence compared to high or low dose LMWH. Finally in the study by Sun et al[47], comparing DOACs with enoxaparin for postoperative VTE

prophylaxis after total hip or knee replacement, Dabigatran was non inferior to enoxaparin in major bleeding incidence.

Dabigatran etexilate, based on the results from our study and from those of previous studies, is a safe alternative to LMWH for postoperative VTE prophylaxis, with a similar rate of major, clinically relevant and minor bleeding.

Bleeding risk of patients receiving dabigatran for atrial fibrillation.

In the study by Healey et al[39], with a population of 4591 patients undergoing various surgeries and procedures, dabigatran compared to warfarin exhibited no difference in bleeding rates in the perioperative period, even when the interruption period was modified. In the other 3 studies[36–38], with a population of 1224 participants having ablation due to atrial fibrillation, dabigatran compared to warfarin exhibited a lower incidence of major or minor bleeding compared to warfarin. Based on these studies[36–38], which are randomized clinical trials with a low risk of bias, dabigatran exhibits a lower major bleeding incidence during the peri ablation period compared to warfarin, whereas it is non inferior to warfarin in the general periprocedural or perioperative period as indicated by Healey et al[39].

In previous studies[20,22,23,48], where dabigatran was compared to warfarin in the periprocedural period of ablation for atrial fibrillation or in the perioperative period the results were similar to our study, except from one study[48]. In the study by He et al[48], where DOACs were compared to warfarin in the perioperative period of various surgeries, Dabigatran exhibited an increased risk of major bleeding. However, the studies that this conclusion was based upon, had certain characteristics that ought to be mentioned. First, the study by Haines et al[49], was a retrospective study, and thus a study with a high risk of bias, and consequently its findings must be interpreted carefully. Secondly, in the puplication by Eikelboom[50] et al, thirty percent of the study population received also aspirin/clopidogrel or their combination, increasing the bleeding potential of Dabigatran. Thus, the result of this study should be taken cautiously into consideration. In a study by Bloom et al[23], with a total population of 17466 patients, no association was established between dabigatran and increased risk of major bleeding when warfarin was used as a comparator. It should be noted though, that in this meta-analysis the studies included were not assessing the bleeding risk in the perioperative period. In a study by Shurrab et al[20], comparing Dabigatran to warfarin in patients undergoing ablation for atrial fibrillation, with a total population of 3481 patients, dabigatran was non-inferior to warfarin in the incidence of major bleeding. Finally, in a study

by Sun et al[22], comparing the use of dabigatran to warfarin in Japanese patients undergoing ablation, Dabigatran was characterized by a lower incidence of major bleeding compared to warfarin.

Furthermore, that data for the administration of dabigatran compared to warfarin in the general perioperative period, according to our search, come mainly from one study by Healey et al[39] which is a sub study not initially designed to assess perioperative events like major bleeding. However, due to the great number of participants, and the study design, the results can be reliably interpreted.

Based on our results, and those from previous studies, apart from one, Dabigatran is characterized by if not a reduced, at least a non-inferior, profile regarding the incidence of major bleeding in the perioperative or periprocedural period.

Perioperative use of Dabigatran compared to Warfarin

Dabigatran etexilate, is a drug that is more easily monitored, as it does not need continuous measurement of lab values to ascertain it's therapeutic range, can be rapidly and safely discontinued according to renal function, and based on the results of various studies, including ours, it has a reduced incidence of major bleeding in the periprocedural period of ablation and is non-inferior to enoxaparin or warfarin in preventing postoperative VTE and causing major bleeding in the perioperative period respectively. Moreover, up until recently the main issue of concern was that it's action could not easily and reliably be reversed[51], as there was no specific antidote. However, with the introduction of Idarucizumab, Dabigatran etexilate can be predictably and completely reversed[52]

Limitations of evidence

Two studies[36,38] were solely performed on Japanese patients and thus their results cannot be safely extrapolated to other ethnic populations. Two studies[37,39] were open-label, and one of them[39], being a sub-study of RE-LY[45], was not designed to assess perioperative bleeding. However, both studies, took several precautions, such as blinded evaluation of outcome events, to reduce the limitations set by the open label design. Two studies[36,37] were not adequately powered to assess the primary outcome.

Limitations of review processes

The major limitation of this review is that it was conducted by one person. Even though the search strategy, study selection and risk of bias was conducted according to a pre-specified plan and an algorithm, selection bias cannot be excluded.

In the studies assessing the peri-ablation period[36–38], there were differences in the preprocedural interruption of dabigatran, thus making it difficult to safely compare their outcomes.

In the studies assessing the VTE prophylaxis, the majority of the population was females, thus extrapolating the results to the male population should be done with caution.

Chapter 5 Conclusion

Dabigatran etexilate is a direct thrombin inhibitor with a favorable pharmacologic profile compared to warfarin. It may be safely administered for the prevention of postoperative VTE after total hip or knee replacement or in the perioperative period as it is non-inferior to low molecular weight heparin or warfarin, respectively, in causing major bleeding. Moreover, it shows a decreased incidence of major bleeding when used in the periprocedural period in patients undergoing ablation for atrial fibrillation.

Chapter 6 References

1. Spyropoulos AC, Brohi K, Caprini J, et al. Scientific and Standardization Committee Communication: Guidance document on the periprocedural management of patients on chronic oral anticoagulant therapy: Recommendations for standardized reporting of procedural/surgical bleed risk and patient-specific thromboembolic risk. *Journal of Thrombosis and Haemostasis*. 2019;17(11):1966-1972. doi:10.1111/jth.14598

2. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation. *Journal of the American College of Cardiology*. 2017;69(7):871-898. doi:10.1016/j.jacc.2016.11.024

3. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in Nonorthopedic Surgical Patients. *Chest*. 2012;141(2):e227S-e277S. doi:10.1378/chest.11-2297

4. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A Novel User-Friendly Score (HAS-BLED) To Assess 1-Year Risk of Major Bleeding in Patients With Atrial Fibrillation. *Chest*. 2010;138(5):1093-1100. doi:10.1378/chest.10-0134

5. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J*. Published online September 29, 2015:ehv476. doi:10.1093/eurheartj/ehv476

6. Fang MC, Go AS, Chang Y, et al. A New Risk Scheme to Predict Warfarin-Associated Hemorrhage. *Journal of the American College of Cardiology*. 2011;58(4):395-401. doi:10.1016/j.jacc.2011.03.031

7. pradaxa-epar-product-information_en-2.pdf.

8. Stangier J, Rathgen K, Stähle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol*. 2007;64(3):292-303. doi:10.1111/j.1365-2125.2007.02899.x

9. Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *EP Europace*. 2021;23(10):1612-1676. doi:10.1093/europace/euab065

10. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and Management of the Vitamin K Antagonists. *Chest*. 2008;133(6):160S-198S. doi:10.1378/chest.08-0670

11. Jacobs LG. Warfarin Pharmacology, Clinical Management, and Evaluation of Hemorrhagic Risk for the Elderly. *Cardiology Clinics*. 2008;26(2):157-167. doi:10.1016/j.ccl.2007.12.010

12. Cropp JS. A Review of Enzyme Induction of Warfarin Metabolism with Recommendations for Patient Management.

13. Breckenridge A, Orme M, Wesseling H, Lewis RJ, Gibbons R. Pharmacokinetics and pharmacodynamics of the enantiomers of warfarin in man. *Clinical Pharmacology & Therapeutics*. 1974;15(4):424-430. doi:10.1002/cpt1974154424

14. Iqbal Z, Cohen M. Enoxaparin: a pharmacologic and clinical review. *Expert Opinion on Pharmacotherapy*. 2011;12(7):1157-1170. doi:10.1517/14656566.2011.570261

15. Fareed J, Hoppensteadt D, Walenga J, et al. Pharmacodynamic and Pharmacokinetic Properties of Enoxaparin: Implications for Clinical Practice. *Clinical Pharmacokinetics*. 2003;42(12):1043-1057. doi:10.2165/00003088-200342120-00003

16. inhixa-epar-product-information_en.pdf.

17. Halvorsen S, Mehilli J, Cassese S, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. *European Heart Journal*. 2022;43(39):3826-3924. doi:10.1093/eurheartj/ehac270

18. Kietaibl S, Ferrandis R, Godier A, et al. Regional anaesthesia in patients on antithrombotic drugs: Joint ESAIC/ESRA guidelines. *European Journal of Anaesthesiology*. 2022;39(2):100-132. doi:10.1097/EJA.0000000000001600

19. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative Management of Antithrombotic Therapy. *Chest*. 2022;162(5):e207-e243. doi:10.1016/j.chest.2022.07.025

20. Shurrab M, Morillo CA, Schulman S, et al. Safety and Efficacy of Dabigatran Compared With Warfarin for Patients Undergoing Radiofrequency Catheter Ablation of Atrial Fibrillation: A Meta-analysis. *Canadian Journal of Cardiology*. 2013;29(10):1203-1210. doi:10.1016/j.cjca.2013.07.005

21. Zhao Y, Lu Y, Qin Y. A meta-analysis of randomized controlled trials of uninterrupted periprocedural anticoagulation strategy in patients undergoing atrial fibrillation catheter ablation. *International Journal of Cardiology*. 2018;270:167-171. doi:10.1016/j.ijcard.2018.06.024

22. Sun Y, Liu X, Xu Y. Meta-analysis of efficacy and safety of new oral anticoagulants compared with warfarin in Japanese patients undergoing catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol*. 2020;58(3):381-399. doi:10.1007/s10840-020-00784-0

23. Bloom BJ, Filion KB, Atallah R, Eisenberg MJ. Meta-Analysis of Randomized Controlled Trials on the Risk of Bleeding With Dabigatran. *The American Journal of Cardiology*. 2014;113(6):1066-1074. doi:10.1016/j.amjcard.2013.11.049

24. Cohen A, Drost P, Marchant N, et al. The Efficacy and Safety of Pharmacological Prophylaxis of Venous Thromboembolism Following Elective Knee or Hip Replacement: Systematic Review and Network Meta-Analysis. *Clin Appl Thromb Hemost*. 2012;18(6):611-627. doi:10.1177/1076029612437579

25. Venker BT, Ganti BR, Lin H, Lee ED, Nunley RM, Gage BF. Safety and Efficacy of New Anticoagulants for the Prevention of Venous Thromboembolism After Hip and Knee Arthroplasty: A Meta-Analysis. *The Journal of Arthroplasty*. 2017;32(2):645-652. doi:10.1016/j.arth.2016.09.033

26. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ*. 2012;344(jun14 1):e3675-e3675. doi:10.1136/bmj.e3675

27. points-consider-clinical-investigation-medicinal-products-prophylaxis-high-intra-post-operative_en-2.pdf.

28. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *Journal of Thrombosis and Haemostasis*. 2010;8(1):202-204. doi:10.1111/j.1538-7836.2009.03678.x

29. Devereaux PJ, Duceppe E, Guyatt G, et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. *The Lancet*. 2018;391(10137):2325-2334. doi:10.1016/S0140-6736(18)30832-8

30. Nagao T, Suzuki H, Matsunaga S, et al. Impact of periprocedural anticoagulation therapy on the incidence of silent stroke after atrial fibrillation ablation in patients receiving direct oral anticoagulants: uninterrupted vs. interrupted by one dose strategy. *EP Europace*. 2019;21(4):590-597. doi:10.1093/europace/euy224

31. Douketis JD, Healey JS, Brueckmann M, et al. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients with an elective surgery or procedure. *Thrombosis and Haemostasis*. Published online 2015.

32. Douketis JD, Healey JS, Brueckmann M, et al. Urgent surgery or procedures in patients taking dabigatran or warfarin: Analysis of perioperative outcomes from the RE-LY trial. *Thrombosis Research*. 2016;139:77-81. doi:10.1016/j.thromres.2016.01.004

33. Yoshida Y, Watarai M, Fujii K, et al. Comparison of uninterrupted anticoagulation with dabigatran etexilate or warfarin in the periprocedural period for atrial fibrillation catheter ablation: Results of the Japanese subgroup of the RE-CIRCUIT trial. *J Arrhythmia*. 2018;34(2):148-157. doi:10.1002/joa3.12024

34. De Caterina R, Procopio A, Lopez Sendon JL, et al. Comparison of Dabigatran Plus a P2Y12 Inhibitor With Warfarin-Based Triple Therapy Across Body Mass Index in RE-DUAL PCI. *The American Journal of Medicine*. 2020;133(11):1302-1312. doi:10.1016/j.amjmed.2020.03.045

35. Ozler T. Comparison of switch therapy modalities (enoxaparine to rivaroxaban or dabigatran) with enoxaparine alone after hip and knee replacement; a non-blinded, randomised study. *Acta Orthop Traumatol Turc*. Published online 2015. doi:10.3944/AOTT.2015.14.0219

36. Nogami A, Harada T, Sekiguchi Y, et al. Safety and Efficacy of Minimally Interrupted Dabigatran vs Uninterrupted Warfarin Therapy in Adults Undergoing Atrial Fibrillation Catheter Ablation: A Randomized Clinical Trial. *JAMA Netw Open*. 2019;2(4):e191994. doi:10.1001/jamanetworkopen.2019.1994

37. Calkins H, Willems S, Gerstenfeld EP, et al. Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation. *N Engl J Med*. 2017;376(17):1627-1636. doi:10.1056/NEJMoa1701005

38. Nin T, Sairaku A, Yoshida Y, et al. A Randomized Controlled Trial of Dabigatran versus Warfarin for Periablation Anticoagulation in Patients Undergoing Ablation of Atrial Fibrillation: DABIGATRAN VERSUS WARFARIN FOR PERIABLATION ANTICOAGULATION. *Pacing and Clinical Electrophysiology*. 2013;36(2):172-179. doi:10.1111/pace.12036

39. Healey JS, Eikelboom J, Douketis J, et al. Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin: Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial. *Circulation*. 2012;126(3):343-348. doi:10.1161/CIRCULATIONAHA.111.090464

40. Eriksson B, Dahl O, Huo M, et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II): A randomised, double-blind, non-inferiority trial. *Thromb Haemost*. 2011;105(04):721-729. doi:10.1160/TH10-10-0679

41. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *Journal of Thrombosis and Haemostasis*. 2007;5(11):2178-2185. doi:10.1111/j.1538-7836.2007.02748.x

42. Eriksson BI, Dahl OE, Büller HR, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *Journal of Thrombosis and Haemostasis*. 2005;3(1):103-111. doi:10.1111/j.1538-7836.2004.01100.x

43. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *The Lancet*. 2007;370(9591):949-956. doi:10.1016/S0140-6736(07)61445-7

44. Oral Thrombin Inhibitor Dabigatran Etexilate vs North American Enoxaparin Regimen for Prevention of Venous Thromboembolism After Knee Arthroplasty Surgery. *The Journal of Arthroplasty*. 2009;24(1):1-9. doi:10.1016/j.arth.2008.01.132

45. Connolly et al. - 2009 - Dabigatran versus Warfarin in Patients with Atrial.pdf.

46. Marcucci M, Etxeandia-Ikobaltzeta I, Yang S, et al. Benefits and harms of direct oral anticoagulation and low molecular weight heparin for thromboprophylaxis in patients undergoing non-cardiac surgery: systematic review and network meta-analysis of randomised trials. *BMJ*. Published online March 9, 2022:e066785. doi:10.1136/bmj-2021-066785

47. Sun G, Wu J, Wang Q, et al. Factor Xa Inhibitors and Direct Thrombin Inhibitors Versus Low-Molecular-Weight Heparin for Thromboprophylaxis After Total Hip or Total Knee Arthroplasty: A Systematic Review and Meta-Analysis. *The Journal of Arthroplasty*. 2019;34(4):789-800.e6. doi:10.1016/j.arth.2018.11.029

48. He H, Ke B, Li Y, Han F, Li X, Zeng Y. Novel oral anticoagulants in the preoperative period: a meta-analysis. *J Thromb Thrombolysis*. 2018;45(3):386-396. doi:10.1007/s11239-018-1612-7

49. Haines DE, Mead-Salley M, Salazar M, et al. Dabigatran versus warfarin anticoagulation before and after catheter ablation for the treatment of atrial fibrillation. *J Interv Card Electrophysiol*. 2013;37(3):233-239. doi:10.1007/s10840-013-9800-z

50. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus Warfarin in Patients with Mechanical Heart Valves. *N Engl J Med*. 2013;369(13):1206-1214. doi:10.1056/NEJMoa1300615

51. Grottke O, Aisenberg J, Bernstein R, et al. Efficacy of prothrombin complex concentrates for the emergency reversal of dabigatran-induced anticoagulation. *Crit Care*. 2016;20(1):115. doi:10.1186/s13054-016-1275-8

52. Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. *N Engl J Med*. 2015;373(6):511-520. doi:10.1056/NEJMoa1502000