

Direct treatment comparison of DAbigatran and Rivaroxaban versus NAdroparin in the prevention of venous thromboembolism after total knee arthroplasty surgery: design of a randomised pilot study (DARINA)

Lucia van der Veen,¹ Jos JAM van Raay,² Carina L E Gerritsma-Bleeker,² Nic JGM Veeger,³ Marinus van Hulst¹

To cite: Veen L van der, van Raay JJAM, Gerritsma-Bleeker CLE, *et al.* Direct treatment comparison of DAbigatran and Rivaroxaban versus NAdroparin in the prevention of venous thromboembolism after total knee arthroplasty surgery: design of a randomised pilot study (DARINA). *BMJ Open* 2013;**3**:e002218. doi:10.1136/bmjopen-2012-002218

► Prepublication history for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2012-002218>).

Received 12 October 2012
Revised 27 November 2012
Accepted 29 November 2012

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see <http://bmjopen.bmj.com>

For numbered affiliations see end of article.

Correspondence to

Lucia van der Veen MSc;
L.vd.veen@MZH.nl

ABSTRACT

Introduction: Two novel agents, dabigatran and rivaroxaban, recently gained market authorisation for prevention of venous thromboembolism (VTE) after hip and knee arthroplasty. However, safety data of the new oral anticoagulants with a long-term use of 42 days are not available for total knee arthroplasty (TKA). Furthermore, there are no clinical trials comparing dabigatran and/or rivaroxaban with nadroparin, which is used in most Dutch departments of orthopaedic surgery. Our aim is to compare the 42-day use of dabigatran and rivaroxaban versus nadroparin after TKA in a clinical explorative pilot study by assessing the incidence of major bleeding and clinically relevant non-major bleeding using a standardised model of bleeding definitions.

Methods and analysis: A randomised open-label pilot study was conducted. Patients ≥ 18 years and weighing more than 40 kg who were scheduled for a primary elective TKA were included. Patients were randomly assigned to three groups. Patients took either a daily oral dose of dabigatran etexilate 220 mg (n=50), 10 mg of oral rivaroxaban (n=50) or subcutaneous nadroparin 0.3 ml (n=50) for 42 days. The primary safety outcome measure was the incidence of bleeding events. Major bleeding events and clinically relevant non-major bleeding events were defined according to accepted guidelines. The secondary measures of this study were the occurrence of VTE, time until the bleeding event, compliance, duration of hospital stay, rehospitalisation, outpatient clinic visits and interventions following complications. Additionally, coagulation monitoring, knee flexion range of motion and Knee injury and Osteoarthritis Outcome Score were evaluated.

Dissemination: The results of this trial provided insight into the validity of design for an adequately powered multicentre study investigating the safety of the new oral anticoagulants compared with nadroparin, an anticoagulant applied for prevention of VTE after knee arthroplasty in the Dutch situation.

Trial registration number: ClinicalTrials.gov: NCT01431456.

INTRODUCTION

After total knee arthroplasty (TKA) surgery, patients are at risk of developing venous thromboembolism (VTE). Approximately one-third of patients with symptomatic VTE manifest pulmonary embolism (PE), whereas two-thirds manifest deep venous thrombosis (DVT) alone. Without thromboprophylaxis, (venographic) DVT can be found in 40–80% of patients.^{1–2} The risk of non-fatal and fatal PE for TKA surgery patients without thromboprophylaxis is 1.8–7.0% and 0.2–0.7%, respectively.³ Hence, thromboprophylaxis is indicated for all patients undergoing TKA. Still, the choice of method raises discussion because treatments that effectively prevent VTE simultaneously increase the risk of bleeding. Patients are, for example, at a higher risk for bleeding when they have hypertension or when they take medication that increases the bleeding risk.^{4–5} Bleeding raises major safety concerns for orthopaedic surgeons who prescribe pharmacological thromboprophylaxis, although the full clinical impact of VTE and its status as a leading cause of preventable death in hospitals remains under-rated.

It is very important to select the most appropriate thromboprophylaxis, by balancing the risk of bleeding versus the prevention of VTE.

Recent research has focused on the development of oral anticoagulants that can be administered in fixed dosages with the expectation that they will provide safe and effective alternatives to existing therapies. Dabigatran etexilate (a direct thrombin inhibitor) and rivaroxaban (a direct factor Xa inhibitor) are new-generation oral anticoagulants. Such new oral agents have already shown efficacy in large-scale clinical trials.^{6–9}

Both medicines have been approved for thromboprophylaxis after TKA in the European Union. Such new oral agents have a rapid onset of action and can be given at fixed doses without the need for routine coagulation monitoring.¹⁰

Meta-analysis comparing the efficacy and safety of dabigatran with enoxaparin suggests that these medicines have a similar efficacy and bleeding rate in patients undergoing hip or knee arthroplasty.^{11 12} Huisman *et al*¹¹ showed that enoxaparin is less effective than rivaroxaban but has a lower risk of bleeding.

In clinical trials the new oral anticoagulants were studied on efficacy and safety with the comparator enoxaparin, a low-molecular-weight heparin (LMWH) preparation.^{6–9} However, the external validity of such clinical trials may be limited for Dutch knee replacement surgery patients. Next to specific LMWH, also the dose and duration vary in clinical practice. More importantly, nadroparin is used in most Dutch departments of orthopaedic surgery after TKA for a treatment period of 42 days. Compared with 10–14 days in market authorisation for dabigatran and rivaroxaban, this is a much longer treatment period.^{13 14}

In this study we chose a treatment period of 42 days for dabigatran, rivaroxaban and nadroparin. First, because a treatment period of 42 days is in compliance with the Dutch guidelines, these guidelines suggest applying prophylaxis with anticoagulants for 6 weeks after arthroplasty.¹⁵ Second, the information on prescription numbers of the manufacturers of dabigatran and rivaroxaban, respectively Boehringer Ingelheim and Bayer, shows that 80% of the Dutch hospitals apply anticoagulants after TKA for a longer treatment period than market authorisation for dabigatran and rivaroxaban. Only 20% of the Dutch hospitals use dabigatran and rivaroxaban, according to the market authorisation duration of 10–14 days. Different guidelines exist regarding the prevention of VTE in orthopaedic surgery. Previous surveys in the Netherlands have revealed that guidelines regarding orthopaedic thromboprophylaxis were not followed and that a wide variation in protocols exists. Of the 84% of approached orthopaedic departments in the Netherlands, 78% used prophylaxis with LMWH. Eighty-five per cent of all these cases continued prophylaxis for 42 days.¹⁶

Third, White *et al*¹⁷ suggested in their study that prolonged prophylaxis may be required, because less is known about the incidence and time course of symptomatic DVT or PE. The authors showed that the risk of developing a DVT or PE decreases when prophylaxis is given for at least 35 days. Moreover, recent clinical trials have demonstrated that more prolonged prophylaxis with LMWH after hospital discharge significantly reduces the incidence of venographically detected DVT after arthroplasty.¹⁸

Given that dabigatran and rivaroxaban have market authorisation on prophylaxis after total hip arthroplasty for a treatment duration of 28–35 h, next to clinical trials on the safety of dabigatran and rivaroxaban after prophylaxis for 35 days after hip arthroplasty,^{19–21} we

expect a similar bleeding risk after 42 days of thromboprophylaxis after TKA. Also the results of the clinical trials on efficacy and safety of dabigatran and rivaroxaban for stroke prevention in atrial fibrillation, with a treatment period longer than 35 days, support the choice and safety of longer treatment duration.^{22 23}

Most orthopaedic departments in the Netherlands generally start perioperative prophylaxis with LMWH between 2 h before and 6 h after surgery. It appears that a preoperative start is no more effective than a postoperative start. A perioperative start is apparently more effective, but this is counterbalanced by a marked increase in the risk of major bleeding in comparison with a preoperative or postoperative regimen.¹⁶ That is the reason we chose postoperative prophylaxis with nadroparin within 6 h after surgery, like the specific departmental protocol on thromboprophylaxis. In order to prevent deviations in medication quality and safety in medication administration, all three study medications were administered within 6 h after TKA. The dose to be administered and the time of first administration of study medication were registered.

In randomised clinical trials the efficacy of a new anticoagulant is typically assessed to establish LMWH prophylaxis. However, safety endpoint definitions applied in these studies can vary. The wide range of definitions used to classify bleeding outcomes in the studies makes it difficult to interpret the comparative bleeding risk associated with the new anticoagulants.^{9 24}

The objective of this study was to compare the 42-day use of dabigatran and rivaroxaban versus nadroparin on safety after TKA. This was an explorative, randomised, open-label, pilot study that assessed the incidence of major bleeding and clinically relevant, non-major bleeding using a standardised model of definitions.²⁵ The purpose of this was to obtain insight into the design validity of an adequately powered multicentre study, investigating the safety of the new oral anticoagulants compared with nadroparin, an anticoagulant applied for prevention of VTE after knee arthroplasty in the Dutch population.

METHODS AND ANALYSIS

Study design

This study was an explorative open-label randomised trial with a three-arm design. A total of 150 patients were included, 50 patients in each treatment group (dabigatran, rivaroxaban and nadroparin). Follow-up lasted for 3 months after a treatment period of 42 days (in total 135 days). **Table 1** presents the schedule of assessments and procedures. This study was approved by the Medical Ethical committee of the Medical Centre Leeuwarden.

Study population

The target population consisted of patients admitted to the hospital for TKA. Patients ≥ 18 years and weighing more than 40 kg who were scheduled for primary elective TKA and provided signed informed consent were eligible for the study.

Table 1 Schedule of assessments and procedures

Week	Outpatient clinic Orthopaedic surgeon	Screen Joint care	Treatment period (days)					Discharge (TKA+5)	TKA +42	Follow-up (by phone) TKA+3 months (135 days)
			TKA -1	TKA +1	TKA +2					
Study period										
Informed consent*		x								
Demographics*	x							x		
Medical history*		x								
Concomitant medication*		x	At any time during the study							x
Physical examination*	x							x		
Blood chemistry*	x		x		x	x		x		
Anticoagulant activity			x			x		x		
Operating parameters*				x						
Dosing info*			At any time during the study							
Bleeding events			At any time during the study							x
DVT or PE*			At any time during the study							x
Other adverse events*			At any time during the study							x
Knee flexion	x						x	x		
KOOS*		x						x		
Compliance								x		
Survival	At any time during the study									

*Standard care.

DVT, deep venous thrombosis; KOOS, Knee injury and Osteoarthritis Outcome Score; PE, pulmonary embolism; TKA, total knee arthroplasty.

Exclusion criteria

Patients were excluded if they met one of the following exclusion criteria:

- ▶ A known inherited or acquired clinically significant active high risk of bleeding or bleeding disorder;
- ▶ Major surgery, trauma, uncontrolled severe arterial hypertension or myocardial infarction within the last 3 months;
- ▶ A history of acute intracranial disease or haemorrhagic stroke;
- ▶ Gastrointestinal or urogenital bleeding or ulcer disease within the last 6 months;
- ▶ Cirrhotic patients with moderate hepatic impairment (aspartate or alanine aminotransferase levels higher than 2× the upper limit of the normal range within the last month);
- ▶ Severe renal insufficiency (creatinine clearance <30 ml/min);
- ▶ Other indications for treatment with anticoagulants;
- ▶ Active malignant disease and
- ▶ Pregnancy or breastfeeding.

Outcomes

Main study endpoint

The primary endpoint of this study was the clinical safety with a 42-day use of the oral once daily unmonitored thrombin inhibitors dabigatran and rivaroxaban versus subcutaneously administered nadroparin by observing the incidence of major bleeding and clinically

relevant non-major bleeding in patients after knee arthroplasty surgery.

Secondary study endpoints

The secondary endpoints of this study were the occurrence of clinical VTE (PE or DVT), time till the bleeding event, compliance, duration of hospital stay, rehospitalisation, outpatient clinic visits and interventions following complications.

Other study parameters

The following patient characteristics were retrieved from the hospital information system, the clinical pharmacy information system or medical records:

- ▶ Demographics (age, sex and weight) and health characteristics (kidney function/estimated glomerular filtration rate, liver function tests, comorbidity);
- ▶ Monitoring anticoagulant activity (anti-Xa activity), activated partial thromboplastin time (aPTT), prothrombin time (PT) and two validated clotting assays developed to measure the anticoagulant activity of rivaroxaban and dabigatran;
- ▶ Knee flexion range of motion, Knee injury and Osteoarthritis Outcome Score (KOOS) scores, obtained from orthopaedic documentation;
- ▶ Medication (time to first dose of DVT-prophylaxis postsurgery, use of NSAIDs, salicylates, SSRIs, clopidogrel, anticoagulants such as VKAs).

Sample size

This study was the first pilot study designed to provide estimates of the bleeding risks associated with the two new anticoagulants dabigatran and rivaroxaban compared with nadroparin in patients admitted to a Dutch hospital for a TKA. The primary purpose was to gather all the relevant information for designing a large-scale multicentre confirmatory clinical trial.

On the basis of the 2009 admission data of the Department of Orthopaedic Surgery in our hospital, it is expected that approximately 350 patients per year will be admitted for a TKA. For the present exploratory pilot study no formal power calculation was performed. A total of 150 patients (50 patients in each arm) were judged sufficient for an initial assessment of bleeding risks associated with the three study treatments, as well as for gathering all relevant information for designing and organising prior to a proposed larger multicentre study.

With this sample size, an estimation of the probability of observing bleeding events can be derived. Different clinical trials on safety of the new oral anticoagulants showed that around 3% of the patients developed a major or non-major clinical bleeding event.^{11 26 27} Assuming this 3% bleeding rate, in our pilot study with 50 subjects per study arm, the probability of observing a major bleeding in at least one patient in each of the three treatment arms was 0.78. The probability of observing two patients with a bleeding event in one of the treatment arms was 0.44.

Randomisation

Patients who met the inclusion criteria were informed about the study, including the study treatments, risks and possible adverse reactions, and the anticipated period of treatment with one of the three prophylactic anticoagulants.

After consenting to participate, patients were allocated to one of the three study arms. At the start of the trial, an independent hospital pharmacist of the local hospital assigned the three medication sequences to a consecutive series of numbers, using a computer-generated randomisation list. On enrolment, each patient was assigned to the next consecutive treatment number and the corresponding study medication was dispensed in an open-label manner. Orthopaedic surgeons were informed about the treatment assignment of their patient.

After closure of the clinical trial a blinded committee adjudicated bleeding events independently by classifying the observed bleeding using information provided by the orthopaedic surgeon and the patient, as described in box 1.

Interventions

Study procedures and the schedule of assessments are displayed in table 1. Patients planning for a TKA surgery were screened for eligibility. If a patient can potentially

be enrolled, he/she was informed about the trial and asked to participate. Having consented to participate, patients were included and received a study identification number, that is, were randomised.

Postoperatively, the patient received the allocated thromboprophylaxis. Patients took either a daily oral dose of dabigatran etexilate (two capsules of 110 mg) 220 mg (n=50) starting with a half-dose (110 mg) within 6 h after surgery (n=50) during 42 days, or 10 mg of oral rivaroxaban once daily, starting within 6 h after surgery during 42 days, or daily subcutaneous nadroparin 2850 IE/ml, 0.3 ml starting within 6 h after surgery during 42 days. The dose to be administered and the time of first administration of study medication during hospital stay were registered.

Patients received standard orthopaedic care (table 1), which included KOOS²⁸ and physiotherapy according to the local standardised protocol. KOOS evaluates the functional status and quality of life of patients with any type of knee injury. Therefore, we wanted to measure the clinical condition of patients before and after treatment, to see if there was any difference in knee function and quality of life between the treatment groups, nadroparin, rivaroxaban or dabigatran. We assume that there will be a relation between clinical relevant (non)-major bleeding and knee function. Physiotherapy was continued until patients reached a full range of motion and an improvement in knee flexion was achieved.

Box 1 Safety criteria for major and minor bleeding (clinically relevant non-major bleeding)

Major bleeding

- ▶ Fatal bleeding
- ▶ Clinically overt bleeding associated with a decrease in the haemoglobin level of more than 20 g/l compared with the pre-randomisation level
- ▶ Clinically overt bleeding leading to transfusion of ≥ 2 units of whole blood or packed cells (according to the CBO guideline: transfusion)
- ▶ Critical bleeding (intracerebral, intraocular, intraspinal, pericardial or retroperitoneal)
- ▶ Bleeding warranting treatment cessation
- ▶ Bleeding located at the surgical site and leading to re-operation or to any unusual medical intervention or procedure for relief (eg, draining or puncture of a haematoma at the surgical site, transfer to an ICU or emergency room)

Minor bleeding (ie, clinically relevant non-major bleeding)

- ▶ Spontaneous skin haematoma $>25 \text{ cm}^2$
- ▶ Wound haematoma $>100 \text{ cm}^2$
- ▶ Spontaneous nose bleeding or gingival bleeding lasting longer than 5 min
- ▶ Spontaneous rectal bleeding creating more than a spot on toilet paper
- ▶ Macroscopic haematuria either spontaneous or, if associated with an intervention, lasting longer than 24 h
- ▶ Other bleeding events considered clinically relevant by the investigator not qualifying as a major bleeding

Every day during hospital stay the patient was examined. Specific attention was given to DVT, PE and bleeding events. All major bleeding events and clinically relevant non-major bleeding events were adjudicated according to the standardised model of bleeding definitions²⁵ (box 1).

After the required standard care, depending on personal recovery, the patient was discharged from the hospital. At discharge, study medications were disposed for up to 42 days after surgery. Patients were informed about the possibility to contact their orthopaedic surgeon or researcher about any adverse events they experienced during or after the treatment with the anticoagulant (in the home situation). On day 4 up until 6 after discharge the patients were contacted daily by an orthopaedic nurse. Bleeding events that occurred in the home situation were all registered, and there was no loss to follow-up.

Patients returned to the outpatient clinic of the hospital after 42 days. This follow-up visit with the orthopaedic surgeon included among other things wound assessment, functional knee range of motion, presence of signs or symptoms of VTE and occurrence of bleeding events.

Three months event-free survival was examined and patients were followed by a telephone interview on DVT or PE adverse events and changes in concomitant medication during the period after treatment with the anticoagulant.

Measurements

Measurements were completed during the preoperative educational session as well as during the inpatient hospital stay. Preoperative, patient demographics, medical history and concomitant medication were registered. Also blood chemistry, knee flexion range of motion and KOOS were measured.

Bleeding assessment

Major bleeding events and clinically relevant non-major bleeding events were defined according to accepted guidelines (see box 1).²⁵ Transfusions of ≥ 2 units of whole blood or packed cells were given according to the CBO guideline: Blood transfusion.²⁹ Bleeding assessment took place during the complete study period of 135 days. Any bleeding events that occurred perceived by patients, researchers, nurses, orthopaedic surgeons or other health workers were registered and defined.

A blinded committee adjudicated bleeding events independently by classifying the description and pictures taken of the observed bleeding.

Efficacy

DVT or PE events that were registered by the orthopaedic surgeon were included in the database. Patients were also informed about the possibility of contacting the orthopaedic surgeon (in the home situation) about any adverse events they experienced during or after treatment with the anticoagulant.

Compliance

Compliance was measured by counting the amount of randomised medication left over after 42 days of treatment.

Coagulation monitoring

Coagulation monitoring was performed by measuring anticoagulant activity (anti-Xa activity), aPTT, prothrombin time (PT) and two validated clotting assays developed to measure the anticoagulant activity of rivaroxaban and dabigatran.

Knee function

Knee flexion range of motion: the flexion range of motion was measured by a goniometer.

Knee injury and Osteoarthritis Outcome Score

The KOOS is a 42-item self-administered questionnaire that includes five dimensions: pain, disease-related symptoms, activities of daily living function, sport and recreation function, and knee-related quality of life measured using a Likert scale (0–4 scale).

Surgery

According to hospital protocol, all the patients were treated under the same surgical conditions, with the same surgical techniques.

Follow-up: event-free survival and questionnaire

Three months event-free survival was reported and patients were asked (by phone) about the DVT or PE events, possible adverse events, changes in concomitant medication and demographics during the period after treatment with the anticoagulant.

Other measurements

The dose to be administered and the time of first administration of study medication were registered.

Time till bleeding event, duration of hospital stay, rehospitalisation, outpatient clinic visits and interventions following complication were registered.

Statistical analysis

The primary analysis focused on risk of bleeding and the occurrence of thromboembolic events in patients treated with dabigatran, rivaroxaban or nadroparin.

The absolute bleeding risk was estimated as an incidence rate with a 95% CI (under the Poisson distribution assumption) for each treatment group. Differences between treatment groups were assessed by Cox proportional hazard regression analysis. In this, specific attention was given to potential differences in the on-treatment versus off-treatment period. Taking into account the single-centre randomised study design, additional multivariable analysis was not foreseen. Kaplan-Meier techniques were used to depict the occurrence of bleeding events over time.

The incidence of thromboembolic events was assessed using the same methodology.

The analysis was based on the intention-to-treat principle. Due to the explorative nature of this pilot study, all p values were interpreted as explorative rather than confirmative.

DISSEMINATION

The results of this trial will provide insight into the validity of design for an adequately powered multicentre study investigating the safety of the new oral anticoagulants compared to nadroparin, an anticoagulant applied for prevention of VTE after knee arthroplasty in the Dutch situation.

Patient recruitment is expected to be finished by the beginning of 2013.

Author affiliations

¹Department of Clinical Pharmacy, Martini Hospital Groningen, Groningen, The Netherlands

²Department of Orthopaedic Surgery, Martini Hospital Groningen, Groningen, The Netherlands

³Department of Epidemiology, University Medical Center Groningen, Groningen, The Netherlands

Contributors LV, MH, CG and JR conceived the idea of the study and were responsible for the design of the study. NV, LV and RH performed the statistical analysis for the study. The initial draft of the manuscript was prepared by LV, MH, JR and NV and then circulated repeatedly among all authors for critical revision. LV was responsible for the acquisition of the data and MH and NV contributed to the interpretation of the results. LV was the coordinator of the study and lead writer. All authors helped plan the study, evolve analysis plans and critically revise successive drafts of the manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None.

Ethics approval Ethical committee of the Medical Centre Leeuwarden (The Netherlands) (RTPO).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Warwick D, Friedman RJ, Agnelli G, *et al*. Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events: findings from the Global Orthopaedic Registry. *J Bone Joint Surg Br* 2007;89:799–807.
- White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107(23 (Suppl 1)):14–8.
- Geerts WH, Heit JA, Clagett GP, *et al*. Prevention of venous thromboembolism. *Chest* 2001;119(1 (Suppl)):132S–75S.
- Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003;107(23 (Suppl 1)):19–16.
- Geerts WH, Bergqvist D, Pineo GF, *et al*. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 (Suppl)):381S–453S.
- Lassen MR, Agno W, Borris LC, *et al*. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776–86.
- Turpie AG, Lassen MR, Davidson BL, *et al*. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009;373:1673–80.
- 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. *J Thromb Haemost* 2007;5:2178–85.
- Ginsberg JS, Davidson BL, Comp PC, *et al*. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009;24:1–9.
- Galanis T, Thomson L, Palladino M, *et al*. New oral anticoagulants. *J Thromb Thrombolysis* 2011;31:310–20.
- Huisman MV, Quinlan DJ, Dahl OE, *et al*. Enoxaparin versus dabigatran or rivaroxaban for thromboprophylaxis after hip or knee arthroplasty: results of separate pooled analyses of phase III multicenter randomized trials. *Circ Cardiovasc Qual Outcomes* 2010;3:652–60.
- Friedman RJ, Dahl OE, Rosencher N, *et al*. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials. *Thromb Res* 2010;126:175–82.
- Toenders WGM Cvz. *CFH-rapport* 08/16, dabigatran (Pradaxa®). College voor zorgverzekeringen, 23 June 2011.
- Graaff van der MCvz. *CFH-rapport* 09/03, rivaroxaban (Xarelto®). 2011 (13) Nederlandse Orthopaedische vereniging. Richtlijn Diagnostiek en Behandeling van heup- en knieartrose. CBO 2007.
- Nederlandse Orthopaedische Vereniging. Richtlijn Diagnostiek en Behandeling van heup- en knieartrose. CBO 2007.
- Ettema HB, Mulder MC, Nurmohamed MT, *et al*. Dutch orthopedic thromboprophylaxis: a 5-years follow-up survey. *Acta Orthopaedica* 2009;80:109–12.
- White RH, Romano RS, Zhou H, *et al*. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med* 1998;158:1525–31.
- Bergqvist D, Benoni G, Gjørgell O, *et al*. Low-molecular-weight-heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med* 1996;335:696–700.
- Eriksson B, 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. *Lancet* 2007;370:949–56.
- Eriksson B, Borris LC, Friedman RJ, *et al*. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *NEJM* 2008;358:26.
- Kakkar AK, Brenner B, Dahl OE, *et al*. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2007;372:31–9.
- ROCKET AF investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. *Am Heart J* 2010;159:340–7.
- Wallentin L, Yusuf S, Ezekowitz MD, *et al*. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;376:975–83.
- Hull RD, Yusen RD, Bergqvist D. State-of-the-art review: assessing the safety profiles of new anticoagulants for major orthopaedic surgery thromboprophylaxis. *Clin Appl Thromb Hemost* 2009;15:377–88.
- European Medicines Agency (EMA). Guideline on clinical investigation of medicinal products for prophylaxis of high intra- and post-operative venous thromboembolic risk (CPMP/EWP/707/98). 15 November 2007.
- Trkulja V, Kolundzic R. Rivaroxaban vs dabigatran for thromboprophylaxis after joint-replacement surgery: exploratory indirect comparison based on meta-analysis of pivotal clinical trials. *Croat Med J* 2010;51:113–23.
- Loke YK, Kwok CS. Dabigatran and rivaroxaban for prevention of venous thromboembolism—systematic review and adjusted indirect comparison. *J Clin Pharm Ther* 2011;36:111–24.
- Groot de IB, Favejee MM, Reijman M, *et al*. The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. *Health Qual Life Outcomes* 2008;6:16.
- CBO richtlijn bloedtransfusie. Kwaliteitsinstituut voor de Gezondheidszorg CBO. Guideline on clinical bloodtransfusions in the Netherlands, 2004.