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Antithrombotic stewardship: a multidisciplinary team approach towards improving antithrombotic therapy outcomes during and after hospitalisation: a study protocol

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ABSTRACT

Introduction: Antithrombotic therapy carries high risks for patient safety. Antithrombotics belong to the top 5 medications involved in potentially preventable hospital admissions related to medication. To provide a standard for antithrombotic therapy and stress the importance of providing optimal care to patients on antithrombotic therapy, the Landelijke Standaard Ketenzorg Antistolling (LSKA; Dutch guideline on integrated antithrombotic care) was drafted. However, the mere publication of this guideline does not guarantee its implementation. This may require a multidisciplinary team effort. Therefore, we designed a study aiming to determine the influence of hospital-based antithrombotic stewardship on the effect and safety of antithrombotic therapy outcomes during and after hospitalisation.

Methods and analysis: In this study, the effect of the implementation of a multidisciplinary antithrombotic team is compared with usual care using a pre-post study design. The study is performed at the Erasmus University Medical Center Rotterdam and the Reinier de Graaf Hospital Delft. Patients who are or will be treated with antithrombotics are included in the study. We aim to include 1900 patients, 950 in each hospital. Primary outcome is the proportion of patients with a composite end point consisting of ≥ 1 bleeding or ≥ 1 thrombotic event from the beginning of antithrombotic therapy (or hospitalisation) until 3 months after hospitalisation. Bleeding is defined according to the International Society of Thrombosis and Haemostasis (ISTH) classification. A thrombotic event is defined as any objectively confirmed arterial or venous thrombosis, including acute myocardial infarction or stroke for arterial thrombosis and deep venous thrombosis or pulmonary embolism or venous thrombosis. An economic evaluation is performed to determine whether the implementation of the multidisciplinary antithrombotic team will be cost-effective.

Ethics and dissemination: This protocol was approved by the Medical Ethical Committee of the

Strengths and limitations of this study

- This will be the first study to determine the effect of a multidisciplinary antithrombotic team in two Dutch hospitals.
- Data will be collected in two different hospitals, accounting for the differences between a university medical centre and a general teaching hospital.
- Improvements may already have been implemented during the preimplementation period because of the nationwide attention to the Landelijke Standaard Ketenzorg Antistolling (LSKA).
- The data collection method may be hampered by recall bias (bleeding and thrombotic events) and response bias (questionnaires).

Erasmus University Medical Center. The findings of the study will be disseminated through peer-reviewed journals and presented at relevant conferences.
Trial registration number: NTR4887; pre-results.

INTRODUCTION

Antithrombotic therapy carries high risks for patient safety.[1–3] The Dutch HARM (Hospital Admissions Related to Medication) study[4] showed that 5.6% of all unplanned hospitalisations in the Netherlands were drug-related and that 46% of these were potentially preventable. Antithrombotics belong to the top 5 medications involved in potentially preventable hospital admissions related to medication.[1–4]

In response to the HARM study, a multidisciplinary guideline was drafted to provide a standard for antithrombotic therapy and to stress the importance of providing optimal care to patients on antithrombotic therapy:

the 'Landelijke Standaard Ketenzorg Antistolling' (LSKA; Dutch guideline on integrated antithrombotic care).[5]

However, the mere publication of this guideline does not guarantee its implementation. A parallel can be drawn with an active policy on reduction of antibiotic resistance: all hospitals are involved in such policies, but recently antibiotic stewardship was only recently proposed in order to further enhance such policies. Multidisciplinary antibiotic teams (A-teams) have been shown to be useful for optimisation of therapy.[6] Analogous to the A-teams, multidisciplinary antithrombotic teams (in Dutch 'Stollingsteam' or S-team) focusing on antithrombotics can be made responsible for LSKA implementation, can provide expertise to support the care of inpatients and outpatients alike, ensure adequate transitioning of patients from the inpatient to the outpatient setting, and improve patient education.

Studies on the implementation and (cost-)effectiveness of a multidisciplinary antithrombotic team are scarce. Antithrombotic services in US hospitals are described mainly as pharmacist-led antithrombotic services that are predominantly aimed at therapy with warfarin.[7] This differs from the Dutch situation, where treatment with VKA (vitamin K antagonists) is mostly carried out by medical doctors in thrombosis services, whereas patients treated with other anticoagulants, such as DOACs (direct oral anticoagulants), are not yet followed systematically. In one survey sent to members of the America College of Pharmacists practice and research networks for cardiology, critical care and general internal medicine, only 4 of 25 responding member centres indicated that their antithrombotic service was multidisciplinary.[7] Padron and Miyares[8] describe an expanded antithrombotic stewardship, including both DOAC treatment and facilitating care after hospital discharge. It concerned a US single-centre pharmacist-directed stewardship. Only a small retrospective control group (n=12) was included in the study. A total of 409 patients on antithrombotics were monitored. Interventions consisted of changes to a more appropriate antithrombotic therapy according to guidelines and dosing corrections. The length of hospital stay was reduced by 1.5 days and cost-savings were $270.320 ($661 per patient) in 1.5 years.[8] Tedders and colleagues evaluated the impact of an inpatient, pharmacist-led dabigatran management protocol. Almost half of the 176 adult patients (46%) required pharmacist intervention related to dabigatran management during hospital admission, particularly for dosing corrections and transitioning between dabigatran and alternative anticoagulants.[9]
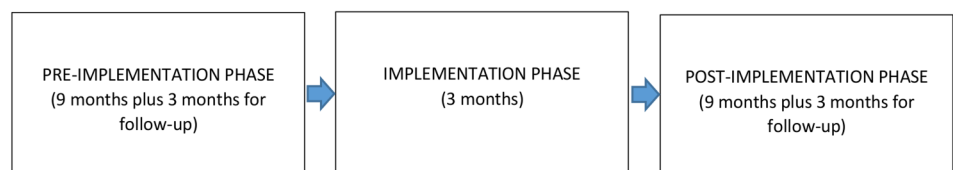
Discharge patient education and promoting patient knowledge with regard to antithrombotic therapy is described in a few studies, but again mostly on warfarin.[10 11]

Given this paucity of evidence on the effect of antithrombotic stewardship, the proposed study aims to determine the influence of hospital-based multidisciplinary antithrombotic stewardship on the effect and safety of antithrombotic therapy outcomes during and after hospitalisation, and the cost-effectiveness of such a multidisciplinary team effort. The null hypothesis is that a multidisciplinary antithrombotic team does not improve the effect and safety of antithrombotic therapy during and after hospitalisation.

METHODS AND ANALYSIS
Study design
A prospective non-randomised before-and-after study, with the intervention being a quality improvement as is mandated by the national guideline LSKA, is performed. The effect between a usual care group (preimplementation measurement) and an intervention group (postimplementation measurement) will be compared. First, patients are included during 9 months in the usual care group (preimplementation phase with 3 months' follow-up). Second, the intervention is implemented (implementation phase of 3 months). Finally, patients are included during 9 months in the intervention group (postimplementation phase with 3 months' follow-up, see figure 1 for flow chart).

Study setting
The study will be performed at the Erasmus University Medical Center (Erasmus MC) and the Reinier de Graaf Hospital. The Erasmus MC is a 1320-bed university medical centre based in Rotterdam. The Reinier de Graaf Hospital is a general teaching hospital located in Delft, the Netherlands with 590 beds. The study will be carried out from 2015 to 2017.

Study population
Patients who are or will be treated with antithrombotics in the Erasmus MC or in the Reinier de Graaf Hospital are eligible for inclusion in the study. In the Reinier de Graaf Hospital, a clinical rule is used to identify the patients, and in the Erasmus MC an email is generated when an antithrombotic is prescribed to the patient. Patients are considered eligible for inclusion if they are using one or more medicines that are listed in tables 1 and 2. Exclusion criteria are the following: (1) no informed consent from the patient (or the parents/guardian of the patient), (2)

Figure 1 Phases during the study.

PRE-IMPLEMENTATION PHASE (9 months plus 3 months for follow-up) → IMPLEMENTATION PHASE (3 months) → POST-IMPLEMENTATION PHASE (9 months plus 3 months for follow-up)

Table 1 Antithrombotics*

Group of antithrombotics (ATC code)	Antithrombotics (ATC code)
Vitamin K antagonists (B01AA)	Phenprocoumon (B01AA04)
	Acenocoumarol (B01AA07)
Heparin group (B01AB)	Heparin (B01AB01)
	Antithrombin III (B01AB02)
	Dalteparin (B01AB04)
	Enoxaparin (B01AB05)
	Nadroparin (B01AB06)
	Danaparoide (B01AB09)
	Tinzaparine (B01AB10)
Direct thrombin inhibitors (B01AE)	Bivaluridin (B01AE06)
	Dabigatran etexilate (B01AE07)
Direct factor Xa inhibitors (B01AF)	Rivaroxaban (B01AF01)
	Apixaban (B01AF02)
Other anticoagulants (B01AX)	Fondaparinux (B01AX05)

*New antithrombotics entering the market are also included in the study when they are introduced in the hospital.
ATC, anatomical therapeutic chemical.

Table 2 Haemostatic agents*

Group of haemostatic agents (ATC code)	Haemostatic agents (ATC code)
Antifibrinolytics (B02AA)	Tranexamic acid (B02AA02)
Vitamin K (B02BA)	Phytomenadione (B02BA01)
Fibrinogen (B02BB)	Fibrinogen, human (B02BB01)
Coagulation factor concentrates (B02BD)	Prothrombin complex concentrate (B02BD01)
	Activated prothrombin complex concentrate (B02BD03)
	Eptacog alfa (activated) (B02BD08)
Antidotes (V03AB)	Protamine (V03AB14)

*New haemostatic agents, including specific antagonist of Xa inhibitors or dabigatran, which may enter the market during our study, will also be included in the study when they are introduced in the hospital.

patients with hospital stays of <24 hours, (3) patients admitted to the intensive care unit, (4) patients treated with low molecular weight heparins only for thrombosis prophylaxis, (5) patients enrolled in a clinical trial of antithrombotic therapy, (6) patients treated with phytomenadione for the prevention and treatment of vitamin K deficiency, (7) patients treated during hospitalisation with a single dose of an anticoagulant medicine. Only the patient's first hospital admission is included in the study period (readmission is an end point).

Study procedures
Usual care
During the preimplementation phase, usual care in both hospitals is provided to patients.

Medication surveillance at admission: The pharmacy software automatically checks the prescribed medication in relation to the medication record that is available within the pharmacy system and automatically generates medication surveillance and signals in case of interactions, overdose, double medication and contraindications.

The automatically generated medication signals (including signals on antithrombotics) are routinely checked during hospital admission by the hospital pharmacist but no structured medication review or pharmacotherapy review is performed.

Patient counselling: At present, resident physicians and nurses are involved in patient instructions on pharmacotherapy. The time spent on medication-related patient instructions is rather limited or is not performed at all. The knowledge necessary for providing adequate instructions is often insufficient in residents and nurses.

Medication reconciliation at discharge: The resident physician prints a prescription or a medication list from the hospital system. The prescription or medication list is sent to the community pharmacist.

The hospital pharmacy is not involved in the discharge of a patient. The medication list provides little or no information on changes in the pharmacotherapy and the reasons for these changes.

Consultation for professionals inside and outside the hospital: In the current situation, hospital residents and/or haematologists are consulted inside the hospital, and hospital pharmacists for specific pharmacotherapeutic issues on antithrombotics. Consultation by professionals outside the hospital is mainly directed towards the haematologists.

Intervention
The intervention consists of the implementation of the multidisciplinary antithrombotic team, which is a quality improvement dictated by the LSKA (Dutch guideline on integrated antithrombotic care). The team in the Erasmus MC will consist of a specialised thrombosis nurse as case manager, a haematologist, a paediatric haematologist, a medical leader regional thrombotic service (responsible for outpatient management of VKA treatment), a hospital pharmacist/clinical pharmacologist, a cardiologist, an anaesthesiologist, a pulmonologist, a neurologist, a surgeon and a quality officer. In the Reinier de Graaf Hospital, the team will consist of a specialised thrombosis nurse as case manager, a haematologist, a medical leader regional thrombotic service, a hospital pharmacist/clinical pharmacologist, a cardiologist, an anaesthesiologist and a neurologist. A pulmonologist, dermatologist, clinical chemist, paediatrician, emergency physician and (orthopaedic) surgeon may be added to the team when necessary.

Medication surveillance at admission: During hospital admission, a structured medication review will be performed daily by the hospital pharmacist/clinical pharmacologist focused on optimising treatment with antithrombotics. The pharmacotherapy review focuses

on dosing (eg, in relation to decreased renal function), double medication, drug–drug interactions, contraindications and perioperative bridging of anticoagulants.

Patient counselling: The purpose of patient empowerment is to provide information and education to patients with the aim of giving the patient more control and responsibility in their own care. Patients need to learn about antithrombotic therapy and how to safely care for it on a daily basis.

Medication reconciliation at discharge: At discharge, medication reconciliation is performed by the specialised thrombosis nurse and the hospital pharmacy. Discrepancies with the preadmission medication are checked using the medication history of the community pharmacy, the appropriateness of the pharmacotherapy is examined, the pharmacotherapy is checked and it is ensured that there is a proper transition to either the thrombotic service or the general practitioner, and to the community pharmacist.

Consultation for professionals inside and outside the hospital: To further support the cooperation between primary care (thrombotic service, the general practitioner and the community pharmacist) and hospital care, consultation is offered by professionals in the multidisciplinary antithrombotic teams.

Drafting of local guidelines: The purpose of drafting local guidelines is to ensure that there is a uniform policy on antithrombotic therapy in the hospital.

Educating physicians, nurses and hospital pharmacists: To increase the knowledge of antithrombotic therapy among physicians, nurses and hospital pharmacists, hospital-wide education is given. The education will assist in providing a uniform antithrombotic policy within the hospital.

Data collection
Outcome measures
The primary outcome of this study is the proportion of patients with a composite end point consisting of ≥1 bleeding (major bleeding and non-major bleeding) or ≥1 thrombotic event from the beginning of antithrombotic therapy (or hospitalisation) until 3 months after hospitalisation. Bleeding is defined according to the International Society of Thrombosis and Haemostasis (ISTH) definitions.

As secondary outcomes, patient-related outcomes and costs will be determined among others. All secondary outcomes are listed below.

The hospital information system is used for collection of the outcome parameters during hospitalisation. For collection of the postdischarge outcomes, validated questionnaires are used. Three months after hospitalisation, the questionnaires are sent to the patient. The patient's general practitioner is asked for bleeding or thrombotic events and readmission when the questionnaires are not returned after one reminder.

For each included patient, data are collected in an electronic case report form (CRF); see table 3 for

detailed information.[12 13] Data are collected during the preimplementation and postimplementation periods. The following parameters are registered:

▶ Major bleeding and non-major bleeding events during and 3 months after hospitalisation: the bleeding events are evaluated and classified by an independent assessment committee consisting of two experts in the field, using the ISTH definitions of bleeding (table 4).[14 15]

▶ Severity and location of bleeding complication: the WHO bleeding scale is used to define the location of the bleeding (oral and nasal, skin, soft tissue, musculoskeletal, gastrointestinal, genitourinary, pulmonary, body cavity, central nervous system, invasive sites and haemodynamic instability).[16] The ISTH definitions (table 4) are used to determine the severity of the bleeding event.

▶ Thrombotic events during and 3 months after hospitalisation: the thrombotic events are evaluated and classified by an independent assessment committee consisting of two experts in the field. A thrombotic event is defined as any objectively confirmed arterial or venous thrombosis, including acute myocardial infarction or stroke for arterial thrombosis and deep venous thrombosis or pulmonary embolism or venous thrombosis. The definitions of terms are listed in table 5.[17–20]

▶ Severity and location of thrombotic complication: the locations of thrombotic events are listed in table 5. The severity of the thrombotic complication is classified as fatal or non-fatal.

▶ Patient data: these are extracted from the medical records of the hospital information system and include date of birth, gender, weight on the first day of hospitalisation, medication use during hospitalisation, laboratory values, (co)morbidities classified according to García-Olmos *et al*[21] and any surgery or diagnosis during hospitalisation.

▶ Readmissions within 3 months after discharge.

▶ The quality of life is measured by the EuroQol EQ-5D (age 16 and older) or EQ-5D-Y (age 4–15) questionnaire.[22–24]

▶ Patients are asked to fill out a questionnaire about their adherence to anticoagulation treatment (Medication Adherence Rating Scale, MARS).[25–28]

▶ The patient satisfaction of the anticoagulation therapy is measured by the visual analogue satisfaction scale.[29]

▶ Adherence by the doctors to the hospital protocol: information from the medical record of the hospital information system is used to verify the adherence by the doctors to the hospital protocol. To determine the adherence to the hospital protocol, the following items are checked: dosing (eg, in relation to decreased renal function, age, body weight), perioperative bridging of anticoagulants, double medication and contraindications.

▶ All-cause mortality: the hospital information system is used to register the date of death and the cause of

Table 3 Data collection: content of CRF

Part	Data content
Patient data	Patient ID
	Date of birth*
	Gender*
	Weight on the first day of hospitalisation*
	Community pharmacist*†
	Reason for hospitalisation*
	Reason for exclusion
	(Co)morbidity*
	Day of hospitalisation*
	Hospital discharge date*
	Any surgery (coded with Verrichtingen code)[12] or diagnosis during hospitalisation*
Study outcomes	Bleeding (major bleeding and non-major bleeding) event(s) during hospitalisation*
	Bleeding (major bleeding and non-major bleeding) event(s) within 3 months after hospitalisation‡
	Severity of bleeding complication
	Location of bleeding complication
	Thrombotic event(s) during hospitalisation*
	Thrombotic event(s) within 3 months after hospitalisation‡
	Severity of thrombotic complication*
	Location of thrombotic complication
	Date of each readmission in the following 3 months after the first hospitalisation*‡
	The reason for readmission‡
	Quality of life (3 months after discharge):†
	▶ Age 0–3: no EQ-5D-Y available
	▶ Age 4–7: EQ-5D-Yproxy V.1
	▶ Age 8–11: EQ-5D-Y or EQ-5D-Y proxy
	▶ V.1
	▶ Age 12–15: EQ-5D-Y or EQ-5D
	▶ Age 16 and older: EQ-5D
	Adherence by the patient to the therapy; MARS5 (3 months after discharge)†
	Patient satisfaction of the antithrombotic therapy; VAS satisfaction scale (3 months after discharge)†
	Adherence to the hospital protocol
	Percentage of TTR of vitamin K antagonists during hospitalisation and as an outpatient during 3 months' follow-up*
	All-cause mortality*§
	Healthcare costs*
Clinical chemistry data	Laboratory values and the date of determination*§
	▶ INR
	▶ APTT
	▶ PT
	▶ dTT
	▶ Hb
	▶ Anti-Xa
	▶ Creatinine
	▶ HT
	▶ Erythrocytes
	▶ Thrombocytes
	▶ eGFR
	▶ Weight
	(Available clinical chemistry data are collected from 3 months before inclusion until 3 months after hospitalisation)
Medication data	Medication use during hospitalisation (coded with ATC code)[13] *
	Use of antidotes: tranexamic acid, phytomenadione, fibrinogen, prothrombin complex concentrate, activated prothrombin complex concentrate, eptacog alfa (activated) and protamine (coded with ATC code)[13] *
	Use of blood products: blood transfusion and other blood products*
	Overview of medication use 3 months before hospitalisation (coded with ATC code)[13]§
	Overview of medication use 3 months after hospitalisation (coded with ATC code)[13]§

*Obtained from the medical record of the hospital information system.
†Obtained from the patient by using a questionnaire.
‡Obtained by sending a small questionnaire asking for visits to the general practitioner or hospital because of a bleeding or thrombotic event within 3 months after hospitalisation.
§Obtained from the community pharmacist and the thrombosis service.
Anti-Xa, antifactor Xa; APTT, activated partial thromboplastin time; CRF, case report form; dTT, diluted thrombin time; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HT, haematocrit; INR, international normalised ratio; MARS, Medication Adherence Rating Scale; PT, prothrombin time; TTR, time in therapeutic range; VAS, visual analogue scale.

Table 4 ISTH definitions of bleeding in patients.

Type of bleeding	Definition of bleeding
Major bleeding in non-surgical patients[14]	1. Fatal bleeding, and/or 2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or 3. Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells
Major bleeding in surgical patients[15]	1. Fatal bleeding, and/or 2. 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, assessed in consultation with the surgeon, and/or 3. Extrasurgical site bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 hours to the bleeding, and/or 4. Surgical site bleeding that requires a second intervention (open arthroscopic, endovascular) or a haemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilisation or delayed wound healing, resulting in prolonged hospitalisation or a deep wound infection, and/or 5. Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause haemodynamic instability, as assessed by the surgeon. There should be an associate fall in haemoglobin level of at least 20 g/L (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 hours to the bleeding.
Non-major bleeding	All bleeding events that do not meet the ISTH criteria according to which major bleeding is defined

ISTH, International Society of Thrombosis and Haemostasis.

Table 5 Definition of thrombotic events

Arterial or venous thrombosis	Definition of the arterial or venous thrombosis
Acute myocardial infarction[17]	Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least one value above the 99th centile URL and with at least one of the following: ▶ Symptoms of ischaemia ▶ New or presumed new significant ST–T changes or new LBBB ▶ Development of pathological Q waves in the ECG ▶ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality ▶ Identification of an intracoronary thrombus by angiography or autopsy
Stroke[18]	An embolic, thrombotic or stroke with motor, sensory or cognitive dysfunction (such as hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) that persisted for 24 or more hours
Deep venous thrombosis[19]	An acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery or autopsy
Pulmonary embolism[20]	The presence of a blood clot in a pulmonary artery with subsequent obstruction of blood supply to the lung parenchyma or if the patient had a ventilation-perfusion scan interpreted as high probability of pulmonary embolism or a positive result on spiral CT, transoesophageal echocardiography, pulmonary arteriography or CT angiography
Any objectively determined arterial or venous thrombus	Non-cerebral, non-cardiac arterial thrombotic or embolic events

cTn, cardiac troponin; LBBB, left bundle branch block; ST–T, ST segment–T wave; URL, upper reference limit.

death. The patient's general practitioner is asked for the date of death and the cause of death 3 months after hospitalisation.

▶ Percentage of time in therapeutic range (TTR) of patients on vitamin K treatment during hospitalisation and as an outpatient during 3 months' follow-up: the international normalised ratio (INR) data during hospitalisation from the electronic medical record are collected by a specialised department in both hospitals. The INR data 3 months after

hospitalisation are obtained from the thrombosis service. TTR is a way of summarising INR control over time. A TTR of 70–80% is desirable,[30] and according to European guidelines, TTR should be above 70%.[31] TTR was calculated according to FR Roosendaal's algorithm with linear interpolation.[32]

▶ Medication use 3 months before and 3 months after hospitalisation: medication records of the community pharmacy can be consulted through a link in the hospital information system for patients who are within the catchment area of the hospital. If a community pharmacist is not connected to the hospital information system, the hospital pharmacy will obtain a faxed medication list from the community pharmacist.

Economic evaluation

The aim of the economic evaluation is to determine whether the implementation of the S-team will be cost-effective. All costs will be calculated from time to start with antithrombotics (or hospitalisation) until 3 months after hospitalisation. Economic analysis will be performed from a healthcare system perspective taking all healthcare costs into account. The costs of the S-team (labour costs and costs for bleeding/thrombotic events (including use of antidotes) will be calculated. All in-hospital (eg, hospitalisation, medication, bleeding and thrombotic events) and outpatient healthcare costs (eg, general practitioner) will be assessed.

Actual medical costs will be calculated by multiplying the volume of healthcare use by corresponding unit prices.

For the intervention, the full cost price will be calculated following the microcosting method,[33] which is based on a detailed inventory and measurement of all resources used. Therefore, costs for all separate actions and time used by all individual healthcare professionals will be calculated for the S-team intervention. For the other healthcare costs, standard cost prices will be used as published in the Dutch guidelines for economic evaluation studies.[34]

To measure the economic impact of the multidisciplinary team approach, cost-effectiveness will be assessed by calculating the incremental cost-effectiveness ratio, defined here as the costs for the intervention (minus savings) divided by the difference in the proportion of patients with a composite end point consisting of ≥1 bleeding (major bleeding and non-major bleeding) or ≥1 thrombotic event during and 3 months after hospitalisation between the intervention and usual care.

Data monitoring

Data are collected on questionnaires (hard copy) and on a CRF using OpenClinica. OpenClinica is an open source clinical trial software for Electronic Data Capture (EDC) Clinical Data Management (CDM). Data entry errors are minimised by using multiple choice options and fixed data fields. In the OpenClinica system, each user is assigned a user type. The data manager submits the data and the monitor checks the conformity of data in CRFs, helping to ensure that the study is complete, accurate and verifiable. OpenClinica validates the file format and performs validity checking for the data. Access to OpenClinica is secured by a password.

Sample size calculation

Annual bleeding rates are 2–3% depending on the type of antithrombotics,[35 36] but in everyday practice it seems that this rate is at least 10%.[37] Conservatively, we will presume a rate of 5%. Annual thrombotic event rates are about 3%.[36] We assume that this is the rate we could achieve with the S-team and that the rate is 4% in the preimplementation period. This results in a composite rate of 9% and we expect to decrease this to a composite rate of 5.5%. With a type 1 error of 0.05, power of 80%, the required sample size will be 917 patients in the preimplementation phase and 917 patients in the postimplementation phase. In order to account for drop-outs, 1900 patients will be included. This calculation is based on annual event rates, although our follow-up is only 3 months. However, since our study is on hospitalised patients (and shortly after hospitalisation), we assume that this presents a period of instability for the patient, leading to relatively high event rates.

Based on the current admission numbers of patients meeting the inclusion criteria, we estimate a total of 30 eligible patients per day in the Erasmus MC. In the Reinier de Graaf Hospital, this is an average of 15 patients per day. Owing to the limited availability of study personnel, it is possible to recruit three patients per day per hospital. A random number generator will be used to select these three patients. With this inclusion rate, we expect to have included the necessary number of patients in a 9 months preimplementation period and in a 9 months postimplementation period.

Data analysis

For the primary end point (the proportion of patients with a composite end point consisting of ≥1 bleeding (major bleeding and non-major bleeding) or ≥1 thrombotic event from the beginning of antithrombotic therapy (or hospitalisation) until 3 months after hospitalisation), interrupted time series analysis is used for data analysis. Baseline data are collected over 3-month separate measurements during a 9-month period, as will be the postimplementation data. The study design thus meets the criteria for a robust interrupted time series analysis, that is three periods of data points preimplementation and postimplementation, each consisting of at least 30 patients.[38–40] The primary outcome will be compared using univariate and multivariate logistic regression. Subanalyses will be performed for each type of antithrombotic and for hospital type in relation to bleeding and thrombotic events. In addition, in-hospital and postdischarge events will be analysed separately. Linear or logistic regression is performed for the

secondary outcomes (frequency of bleeding events, frequency of thrombotic events, severity of bleeding complications, length of hospital stay, readmissions, quality of life, adherence by the patient to the therapy, patient satisfaction with antithrombotic therapy, adherence to the hospital protocol, healthcare costs, all-cause mortality and the percentage of time in a therapeutic range of VKA). To assess whether differences between preimplementation and postimplementation periods may be explained by other factors, that is, differences in patient characteristics for the two periods, will also be compared with the use of the appropriate test (t-test, Mann-Whitney U test or Pearson's χ^2 test).

ETHICS AND DISSEMINATION
Ethical approval
This study is registered in the Dutch Trial Registry for clinical trials (record number NTR4887) on 3 November 2014.[41] All participants will provide written and informed consent and can withdraw from the study at any time.

Dissemination
The findings of the study will be disseminated through peer-reviewed journals and presented at relevant conferences.

DISCUSSION
Antithrombotic therapy carries high risks for patient safety, mainly bleeding episodes. Multidisciplinary teams have been proposed to improve the safety of antithrombotic therapy. However, most antithrombotic services are described mainly as pharmacist-led antithrombotic services in US hospitals that are predominantly aimed at warfarin dosing, which differs from the Dutch situation. In this study, we want to determine the effect of a multidisciplinary antithrombotic team on the frequency of a composite end point consisting of bleeding and thrombotic events in two Dutch hospitals. The design of this study has several strengths. First, we have gained experience with the data collection procedure due to a previous pilot project at the Reinier de Graaf Hospital. Therefore, we were able to optimise study procedures such as collection of the outcome parameters. Second, we will investigate the effect of the team in two different hospitals, at the Erasmus MC and the Reinier de Graaf Hospital, accounting for the differences between a university medical centre and a general teaching hospital. This will enhance the generalisability. Third, a substantial number of patients are to be included. We anticipate having little problems in recruiting patients in order to ensure sufficient statistical power which should enable us to measure the primary outcome. A fourth strength of this study is the patient empowerment intervention. Empowerment of the patient increases their autonomy and involvement in their care and treatment. Fifth, we are also conducting a cost-effectiveness assessment.

Finally, the multidisciplinary antithrombotic team is offering consultation for professionals both inside and outside the hospital.

This study also has some limitations. First, studies using questionnaires for collection of several secondary outcomes may suffer from response bias. This will be minimised as much as possible by contacting the patients by telephone when the questionnaires are not returned within 2 weeks. Second, despite the fact that this is a multicentre study, only two hospitals are included. Third, in obtaining the patient data, we are dependent on the information in the medical records. Fourth, introducing recall bias for minor bleeding and thrombotic events. Fifth, the sample size calculation is based on annual event rates, although our follow-up is only 3 months. This is justified by the assumption that the period during and shortly after hospitalisation represents a period of instability for the patient, leading to a relatively high frequency of events. Yet we have no literature data to support our assumption, so the sample size may prove to be too small. Finally, it is a prospective nonrandomised before-and-after study, without a retrospective control group. Improvements may already have been implemented during the preimplementation period because of the nationwide attention to the LSKA. However, by time series analysis, we mean to adjust for this effect.

In conclusion, the main objective of this study is to assess the effectiveness of a multidisciplinary antithrombotic team with the aim of reducing the frequency of a composite end point consisting of bleeding and thrombotic events. If such a team proves to be effective, implementation in hospitals will be recommended.

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