ALBERT DREIJER

ANTITHROMBOTIC STEWARDSHIP

Antithrombotic stewardship

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COLOPHON

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Voor pa

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Chapter 1

General Introduction

GENERAL INTRODUCTION

Anticoagulant drugs are widely used for the prevention and treatment of venous and arterial thrombosis [1,2]. In the Netherlands, approximately 400,000 patients are currently being treated with vitamin K antagonists (VKAs) [3]. The most frequently used VKAs in the Netherlands are acenocoumarol and phenprocoumon. The main difference between those two drugs is the half-life; acenocoumarol has a short half-life (2-8 h) and phenprocoumon a long half-life (156-178 h) [4]. Despite the fact that VKAs are still the most commonly used type of anticoagulant, the use of direct oral anticoagulants (DOACs) including dabigatran, rivaroxaban, apixaban and edoxaban is increasing in the Netherlands [3]. The major advantages of DOACs are the greater ease of use, because there is no need for routine laboratory monitoring and DOACs are administered in a fixed dose. In addition, there are fewer drug and food interactions and a wider therapeutic window of DOACs compared to VKAs [5]. Despite the advantages of DOACs over VKAs, there are also some disadvantages. DOACs are mainly eliminated through the kidneys, resulting in DOACs being contraindicated in patients with severe renal dysfunction [6]. Moreover, DOACs are contraindicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk [7]. Van der Hulle et al. have demonstrated DOACs to be at least as effective as VKAs in the treatment of venous thrombo-embolism (VTE) [8]. Another meta-analysis of phase 3 randomized controlled trials comparing DOACs with VKAs for treatment of VTE showed reductions in important components of major bleeding, such as fatal bleeding and intracranial bleeding in patients treated with DOACs [9]. The same results regarding intracranial bleeding were found in atrial fibrillation (AF) trials [10]. However, the AF trials showed an increased risk of major gastrointestinal (GI) bleeding in DOAC users [10]. Post-market studies confirm this, but also show that more than 90% of GI bleeding in DOAC users are not life-threatening [11]. Besides VKAs and DOACs, low-molecular weight heparins (LMWHs) are frequently used anticoagulants. LMWHs are used for treatment of VTE and in lower doses as thromboprophylaxis [12]. This thesis focuses on the therapeutic doses of LMWHs which are mainly used for initial treatment of VTE, bridging during perioperative interruption of VKA treatment and for cancer-associated VTE. Antiplatelet therapy plays an important role in the treatment of arterial thrombosis. They are widely used in primary and secondary prevention of thrombotic cerebrovascular and cardiovascular diseases and are sometimes used simultaneously with anticoagulant drugs to prevent recurrent thrombotic complications [13].

Although therapy with anticoagulants is highly effective, they are one of the most common drug classes involved in medication errors and adverse events [14-16]. The Dutch HARM (Hospital Admissions Related to Medication) study showed that 5.6% of

all unplanned hospitalizations were drug-related and that anticoagulants belong to the top 5 medications involved in potentially preventable hospital admissions related to medication [17]. On the one hand, during the use of anticoagulants, thrombosis may still occur. During therapeutic use of anticoagulants, recurrent VTE generally occurs in approximately 2% of VTE patients per year [8]. On the other hand, bleeding is the most serious and common complication of treatment with anticoagulants. Major bleeding occurs in 2-5 per 100 patients per year during treatment with therapeutically dosed anticoagulants and are fatal in about 24% of cases [18-20]. Because of this high risk of bleeding, anticoagulants should not be used or only used with caution in patients with a high risk of bleeding. Therefore, it is essential that determinants of a high bleeding risk are identified. The small therapeutic range of anticoagulants also increases the risk of harm when medication errors occur with this class of drugs. Insight in medication errors and their potential causes may further help to decrease the risk of bleeding or recurrence of VTE.

DETERMINANTS FOR BLEEDING

Potential risk factors associated with bleeding and anticoagulation-related medication errors have been intensively studied. Potential risk factors for bleeding include advanced age, female gender [21,22], comorbidities, (such as cancer, hypertension, diabetes, renal impairment, anemia), previous bleeding, genetic polymorphism, and concomitant use of interacting drugs [23-28]. These risk factors are mostly studied in outpatients treated with VKAs for specific indications, such as AF or VTE [23-27]. Hospitalized patients may be especially at risk for bleeding, for instance due to start of additional medication influencing the metabolism of anticoagulants and because of (surgical) interventions. The prevalence and potential risk factors for bleeding in hospitalized patients on anticoagulant therapy is largely unknown. Furthermore, studies on the translation of the individual potential risk factors into a clinical prediction model for the risk of an INR ≥ 4.5 in hospitalized patients are scarce. An INR ≥ 4.5 is an adequate marker for an increased risk of bleeding because 4.5 is the level at which the risk of bleeding increases sharply. Existing prediction models, such as the HAS-BLED score, are derived from cohorts of patients in ambulatory care or ambulatory and hospitalized patients together and focus especially on patients with a specific indication (i.e. AF or VTE) [23,25,29,30]. A model predicting the risk of an INR ≥ 4.5 in a general hospitalized population based on risk factors that are electronically collected during routine care could help to focus safety interventions on high risk patients.

MEDICATION ERRORS WITH ANTICOAGULANTS

The 1999 Institute of Medicine report, 'To Err is Human,' stated that 44,000–98,000 hospitalized patients in the USA die each year because of medical errors [31]. A medication error is defined as any preventable event that may cause or lead to inappropriate medication usage or patient harm [32]. Medication errors may occur during the prescribing, transcribing and verifying, dispensing, administering and monitoring phases of the medication process [31]. A few studies characterized anticoagulant medication errors. Fanikos et al. found that errors during drug administration were most often seen, whereas Winterstein et al. and Samsiah et al. reported the medication errors mainly occurred during the prescribing phase [33-35]. Most previous studies focused on medication errors in outpatients associated with warfarin or LMWH and do not concern patients using acenocoumarol, phenprocoumon or DOACs [33,36]. Despite anticoagulants frequently being involved in medication errors, the prevalence and characteristics of anticoagulation-related medication errors in hospitals and primary care are largely unknown.

ANTITHROMBOTIC STEWARDSHIP

In response to the Dutch HARM study [17], a multidisciplinary guideline was drafted to provide a standard for anticoagulant therapy and to stress the importance of providing optimal care to patients on anticoagulant therapy: the 'Landelijke Standaard Ketenzorg Antistolling' (LSKA; Dutch guideline on integrated antithrombotic care) [37]. The LSKA describes the tasks and responsibilities and how the communication between healthcare providers and the patient should be organized at a regional level. However, the publication of the LSKA guideline does not guarantee its implementation. Active methods are needed to improve the implementation and awareness of the guideline. Multidisciplinary antithrombotic teams (in Dutch 'Stollingsteams' or S-teams) can be made responsible for LSKA implementation and help to focus safety interventions, as dictated in the LSKA guideline, thereby improving the effect and safety of anticoagulant therapy. The safety interventions (education, medication reviews, drafting of local anticoagulant therapy guidelines, patient counseling and medication reconciliation at admission and discharge) as described in the LSKA will be discussed in more detail.

Education

Prescribing of medication is a complex and challenging task. Prior studies showed that the majority of reported anticoagulation medication errors occurred in the prescribing phase of the medication process [33-35,38-40]. In the hospital, the majority

of drugs are prescribed by junior doctors who are relatively inexperienced [41,42]. Educating physicians, nurses and hospital pharmacists may increase the knowledge of anticoagulant therapy which will thereby improve prescribing performance.

Medication reviews by hospital pharmacists

Another strategy to improve the efficacy and safety of anticoagulant therapy is by performing medication reviews, defined as a systematic assessment aiming to evaluate and optimize medication of an individual patient [43]. Bajorek et al. implemented a pharmacist-coordinated multidisciplinary review process in a hospital setting to optimize anticoagulant use in elderly atrial fibrillation patients. As a result of the intervention, 35.8% (78 out of 218) of the patients required changes to their existing anticoagulant therapy [44]. However, most studies concerned patients treated with warfarin and the impact on clinical outcomes such as bleeding and thrombotic events in anticoagulant users is rarely reported.

Anticoagulant therapy guidelines

Guidelines and protocols are developed to improve prescribing quality and thus patient outcomes [45]. However, a gap between recommended care and clinical daily practice exists [46]. The adherence to guidelines by prescribers is inconsistent [47-51]. Several strategies to improve guideline adherence have been described [52-54]. Education programs and computer-based clinical decision support systems showed significant improvements in adherence to guidelines for venous thromboembolism in hospitals [52]. Bos et al. showed that education of prescribers in the hospital combined with audit and feedback by the hospital pharmacist reduced non-adherence to guidelines covering pain management, antithrombotics, fluid and electrolyte management, application of radiographic contrast agents and surgical antibiotic prophylaxis [53]. Nevertheless, results from previous studies showed that there is still room for improvement of adherence to guidelines.

Patient counseling

The purpose of patient empowerment is to provide education to patients with the aim of helping patients to get more control and responsibility over their own health [55-57]. The impact of empowerment on health outcomes, patient satisfaction, self-efficacy and adherence has been demonstrated earlier [58-61]. McAllister et al. showed that empowerment leads to better health outcomes, especially with regard to chronic conditions [58]. Furthermore, empowered patients are more satisfied and also have a higher self-efficacy. Main reasons for these improvements are the increase in knowledge and control over their health care [59-61]. Hearnshaw et al. found that

empowerment had a positive effect on adherence to the treatment due to the increase of patients' autonomy [62]. To date, no studies on the effect of patient empowerment in anticoagulant users have been performed.

Medication reconciliation

Approximately 46% of all medication errors occur during the patient's hospital admission or discharge [63]. Main causes for these medication errors are poor communication and documentation of medical information [63-65]. Medication reconciliation, defined as the process of creating the most complete list of a patient's current medication, may improve the continuity of pharmaceutical care during hospital admission, discharge, and restart of medication after a surgical intervention [66]. Since many different healthcare providers are involved in anticoagulation care and medication is changed regularly during hospitalization (e.g. due to start of additional medication influencing the metabolism of anticoagulants and because of (surgical) interventions or bleedings) medication reconciliation of patients using anticoagulants is necessary, and should also involve communication on INR range, duration of therapy and indication (e.g. in relation to dual or triple therapy).

Studies on the implementation and effectiveness of a multidisciplinary antithrombotic team are scarce. Most studies concentrate on patients treated with warfarin [67,68] for specific indications, such as AF or VTE [44,54,69], which differs from the Dutch situation where most patients are treated with DOACs and other VKAs. Antithrombotic teams are reported to be mainly pharmacist-led antithrombotic teams [44,67,68,70] and focused on surrogate endpoints such as compliance to anticoagulant protocols, readmissions, patient care and transitioning of patients on anticoagulation to outpatient management [54,71,72]. Moreover, most studies used a pre-post analysis to determine the impact of antithrombotic teams, which does not evaluate the longitudinal effect of the intervention [73]. There is a need for studies with a more robust study design, to determine the influence of a multidisciplinary approach with associated interventions on the effect and safety of anticoagulant therapy outcomes.

OBJECTIVE OF THIS THESIS

The main objectives of this thesis are to identify determinants for bleeding in hospitalized patients treated with anticoagulant therapy and to characterize anticoagulation-related medication errors (part 1). In addition, to determine the effect of antithrombotic stewardship on bleeding complications and thrombotic events and adherence to anticoagulant guidelines among prescribing physicians (part 2).

OUTLINE OF THESIS

Part 1

The first part of this thesis focuses on determinants for bleeding and anticoagulant medication errors.

In **chapter 2** a clinical prediction model for the risk of an international normalized ratio (INR) ≥ 4.5 in patients admitted to medical or surgical wards who are treated with VKAs will be developed and validated.

Previous studies have identified risk factors of bleeding in outpatients treated with VKAs, but data on the prevalence and potential risk factors of bleeding in hospitalized patients are lacking. Therefore, we will determine the prevalence of bleeding in anticoagulant users during hospitalization and identify potential risk factors of bleeding in hospitalized patients treated with anticoagulant therapy in **chapter 3**.

Despite the fact that anticoagulants are frequently involved in medication errors, little is known about the characteristics of anticoagulation-related medication errors reported in hospitals and primary care. Therefore, in **chapter 4** we will determine and characterize the proportion of anticoagulant medication error reports in Dutch hospitals and primary care.

Part 2

The second part of this thesis focuses on interventions to improve the effect and safety of antithrombotic therapy.

In **chapter 5** the study protocol of the antithrombotic stewardship study is described in detail. In **Chapter 6** we determine the effect of antithrombotic stewardship on the effect and safety of antithrombotic therapy during and after hospitalization.

Guidelines and protocols are developed to improve prescribing quality, but adherence is often suboptimal. Therefore, in **chapter 7** we determine the effect of antithrombotic stewardship on adherence to anticoagulant guidelines among prescribing physicians.

In the general discussion, **chapter 8**, the results of the different studies are discussed. Implications for clinical practice and recommendations for future anticoagulant treatment are given. In **chapter 9** a summary of this thesis is given.

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Part 1/2

Determinants of bleeding and anticoagulant medication errors

2. Development of a clinical prediction model for an international normalised ratio ≥ 4.5 in hospitalised patients using vitamin K antagonists

3. Risk of bleeding in hospitalized patients on anticoagulant therapy: prevalence and potential risk factors

4. Anticoagulant medication errors in hospitals and primary care: a cross-sectional study

Chapter 2

Development of a clinical prediction model for an international normalised ratio ≥ 4.5 in hospitalised patients using vitamin K antagonists

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SUMMARY

Vitamin K antagonists (VKAs) used for the prevention and treatment of thromboembolic disease, increase the risk of bleeding complications. We developed and validated a model to predict the risk of an INR ≥ 4.5 during hospital stay. Adult patients admitted to a tertiary hospital between 2006 and 2010 treated with VKAs were analyzed. Bleeding risk was operationalized as an INR value ≥ 4.5. Multivariable logistic regression analysis was used to assess the association between potential predictors and an INR ≥ 4.5 and validated in an independent cohort of patients from the same hospital between 2011 and 2014. We identified 8,996 admissions of patients treated with VKAs, of which 1,507 (17%) involved an INR ≥ 4.5. The final model included the following predictors: gender, age, concomitant medication and several biochemical parameters. Temporal validation showed a c statistic of 0.71. We developed and validated a clinical prediction model for an INR ≥ 4.5 in VKAs treated patients admitted to the hospital. The model includes factors that are collected during routine care and are extractable from electronic patient records, enabling easy use of this model to predict an increased bleeding risk in clinical practice.

INTRODUCTION

Vitamin K antagonists (VKAs) are frequently used medications in the prevention and treatment of thromboembolic disease (Ansell *et al*, 2008; Wysowski *et al*, 2007). However, the benefit of their use is partially offset by the increased risk of bleeding complications. The reported overall risk of major bleeding complications is 1.4-2.1 per 100 person years of VKA treatment (Palareti *et al*, 1996; Schulman *et al*, 2008; Roskell *et al*, 2012).

The risk of bleeding is related to the international normalized ratio (INR) and is influenced by many factors, such as dietary intake of vitamin K, concomitant medication, comorbidities and genetic factors (Schulman *et al*, 2008). Although numerous risk factors have been linked to a higher bleeding risk, it is difficult for physicians to assess the risk of bleeding by VKAs for an individual patient. Prediction models could help physicians to predict VKA-associated bleeding complications and make more accurate assessments which may lead to adjustments in therapy or closer monitoring.

Prediction models for bleeding complications or a supratherapeutic INR in patients on VKA therapy can be found in literature (Beyth *et al*, 1998; Kuijer *et al*, 1999; Gage *et al*, 2006; Shireman *et al*, 2006; Ruiz-Gimenez *et al*, 2008; Pisters *et al*, 2010; Fang *et al*, 2011; Hippisley-Cox Focks *et al*, 2014). Since bleeding itself is often not registered electronically, supratherapeutic INR can be used as a substitute as this is a proven risk factor for bleeding complications (Palareti *et al*, 1996; Amouyel *et al*, 2009; Hylek *et al*, 2003). Generally, these prediction models include comorbidities, such as hypertension (Gage *et al*, 2006; Pisters *et al*, 2010; Fang *et al*, 2011; Hippisley-Cox Focks *et al*, 2014), history of stroke (Beyth *et al*, 1998; Gage *et al*, 2006; Pisters *et al*, 2010), prior bleeding (Beyth *et al*, 1998; Gage *et al*, 2006; Shireman *et al*, 2006; Pisters *et al*, 2010; Fang *et al*, 2011), malignancy (Kuijer *et al*, 1999; Gage *et al*, 2006; Ruiz-Gimenez *et al*, 2008), genetic polymorphism (Gage *et al*, 2006) or fall risk (Gage *et al*, 2006). These are mainly risk factors that are not easily extractable from electronic medical records (EMRs). Therefore, the available prediction models cannot be implemented as electronic clinical decision support rules ('clinical rules'). Yet, the application of such rules would greatly assist physicians to identify patients for whom the risk of bleeding is high.

Furthermore, most models focus on patients with a specific indication, such as atrial fibrillation (AF) (Gage *et al*, 2006; Shireman *et al*, 2006; Pisters *et al*, 2010; Fang *et al*, 2011; Focks *et al*, 2016) or venous thromboembolism (VTE) (Kuijer *et al*, 1999; Ruiz-Gimenez *et al*, 2008), and are derived from cohorts of patients in ambulatory care (Beyth *et al*, 1998; Ruiz-Gimenez *et al*, 2008; Fang *et al*, 2011), or ambulatory and hospitalized patients together (Kuijer *et al*, 1999; Gage *et al*, 2006; Pisters *et al*, 2010).

Factors associated with the occurrence of bleeding in non-selected patient populations during hospital stay might be different from those during ambulatory care. Existing prediction models for bleeding events in patients using VKAs are not applicable for clinical rules and do not concern the general hospitalized population.

Therefore, we aimed to develop a model predicting the risk of an INR ≥ 4.5 during hospital stay, for adult patients who are treated with VKAs, based on risk factors that are electronically collected during routine care.

METHODS

Study design

This study is designed as a cohort study. Data were prospectively recorded and retrospectively analyzed. The medical ethics committee granted permission for this study.

Study setting

The study is conducted in the Erasmus University Medical Center (Erasmus MC). The Erasmus MC is a 1320-bed University Medical Center based in Rotterdam, the Netherlands.

Study population

Patients aged 18 years and older who were admitted to the Erasmus MC between January 2006 and December 2010 and treated with vitamin K antagonists (VKAs) were included in the study. The VKAs used are acenocoumarol (B01AA07) and phenprocoumon (B01AA04). These are the most commonly used VKAs in the Netherlands. Exclusion criteria were the following: (1) patients with an admission to the intensive care unit (ICU), (2) patients without an INR measurement during their treatment with a VKA, (3) patients with an INR ≥ 4.5 as reason for hospitalization which is defined as the occurrence of an INR ≥ 4.5 within 12 hours after hospitalization.

Patients were considered at risk in the period between start of the prescription of the VKA until the end of the hospital prescription, plus a wash out period. The wash out period of a maximum of 5 times the elimination half-life was set to five days for acenocoumarol and fourteen days for phenprocoumon (Palareti *et al*, 1996).

Data collection

The hospital information system was used for data collection (Table S1). Patient data were coded according to Dutch privacy guidelines. Bleeding risk was operationalized as INR ≥ 4.5. Data were collected from start of VKA treatment until the first occurrence of an INR ≥ 4.5 or until the end of exposure to VKAs, discharge, in hospital death, or until the end of the study (31 December 2010 for the development cohort and 31 December 2014 for the validation cohort), whichever came first.

Candidate predictors

The following candidate predictors were included in the analysis: gender, age, occurrence of an INR ≥ 4.5 during a previous admission (yes/no), type of VKA (acenocoumarol/phenprocoumon), concomitant use of known interacting drugs and type of ward (medical/surgical). The cardiology wards, internal medicine wards, oncology wards and psychiatry wards were classified as 'medical', and the surgical wards, ear-nose-throat and eye surgery wards were classified as 'surgical'. We also considered the most recently (with a maximum of 7 days) measured laboratory value in the week before start of VKA therapy of alanine amino transferase (ALAT), aspartate amino transferase (ASAT), gamma-glutamyl transferase (y-GT), lactate dehydrogenase (LDH), albumin, estimated glomerular filtration rate (e-GFR) calculated with the modification of diet in renal disease (MDRD) formula, hemoglobin (Hb), creatinine, thyroid stimulation hormone (TSH), triiodothyronine (T3), thyroxin (T4), c-reactive protein (CRP), platelet count (Plt) and leucocytes (Leu).

We defined concomitant use of known interacting drugs as an active prescription at the same time the VKA was prescribed, or when the interacting drug was stopped before start of VKA but within the wash out period of a maximum of 5 times the elimination half-life of the interacting drug (Palareti *et al*, 1996). The following drugs were considered as interacting drugs that increase the effect of VKAs the most; miconazole, cotrimoxazole, fluconazole, voriconazole and amiodarone. Rifampicin, carbamazepine, phenytoin, colestyramin and anti-thyroid drugs were considered to decrease the effect of VKAs the most (De Federatie van Nederlandse Trombosediensten).

Statistical analysis

All data were analyzed using R (The R Foundation for Statistical Computing, Vienna, Austria). Missing values of candidate predictors were filled in with multiple imputation (MI). Each missing value was imputed ten times. Imputed values were drawn from the predictive distribution in an imputation model that included all candidate predictors and the outcome (INR ≥ 4.5). MI resulted in ten complete datasets, which were

analyzed with standard data methods. The results were combined to produce overall estimates and standard errors that reflect missing data uncertainty (Van Buuren *et al*, 2006). Univariable and multivariable logistic regression analysis was used to assess the association of candidate predictors with the risk of an INR ≥ 4.5. Since some patients were included multiple times for the recreation of our model we used random effect modeling (Harrell, 2001). For the continuous predictor age, a linear relationship with outcome was found to be a good approximation after assessment of nonlinearity using restricted cubic splines (Harrell, 2001). Age was included as piecewise linear with two pieces, up to 60 years and above 60 years, for a better description of the shape of the association with an INR ≥ 4.5. Some laboratory values (LDH and CRP) were log transformed for the same reason. Odds ratios for continuous variables were given for the 75 percentile versus 25 percentile of the variable. Using a backward elimination strategy with $p < 0.15$, the strongest prognostic factors were included in the final model (Steyerberg, 2008).

Internal validation

Despite the large cohort (N=8,996), the number of events were limited (N=1,507). Therefore we used bootstrap resampling to adjust for possible over fitting and optimistic performance of the model. One hundred bootstrap samples were drawn with replacement; a prognostic model was developed in each sample; and the performance was evaluated in the bootstrap sample and in the original sample. The average calibration slope of the bootstrap procedure was used to shrink the regression coefficients in the final model. The resulting final model was applied in an Excel risk calculator. The discriminative ability of the model was assessed with the concordance statistic (c-statistic). Calibration was assessed with the calibration intercept and slope.

External validation

In order to validate the clinical prediction model, it was applied to a separate cohort of patients who were treated with VKAs and admitted to medical or surgical wards between 2011 and 2014 in the Erasmus MC. These patients were enrolled according to the same criteria as the patients in the development cohort.

RESULTS

Cohort description

In the study 8,996 admissions of 6,073 individual patients treated with VKAs were included (Table 1). The median length of stay per admission was 6 days (interquartile

range 3-11). The median age was 72 (interquartile range 62-82) years and 41% of patients were female. Acenocoumarol was prescribed more often (in 89% of admissions) than phenprocoumon (in 11% of admissions). We identified 1,507 admissions (17%) with an INR ≥ 4.5 for 1,112 individual patients.

Prediction model

After multivariate analysis, the following variables were identified as predictors: gender, age, ALAT, albumin, e-GFR, and the natural logarithm (Ln) of: LDH and CRP. The strongest predictors for an INR ≥ 4.5 during hospitalization were concomitant use of miconazole, cotrimoxazole, fluconazole, voriconazole, amiodarone or antithyroid drugs. The values for odds ratio (OR) and the 95% confidence intervals are shown in Table 2. The predicted risk of an INR ≥ 4.5 during hospital stay can be calculated using the formula stated in Table III. TSH, T3 and T4 had too many missing values and were excluded from the analysis. The variables for which laboratory values were missing are listed in Table S2.

Internal validation

Bootstrapping resulted in a shrinkage factor of 0.95. The *c*-statistic was 0.72 before and 0.71 after shrinkage, which shows our initial model had only minor optimism.

External validation

We identified 1,227 admissions (14%) with an INR ≥ 4.5 for 1,052 individual patients in the validation cohort. External, temporal validation resulted in a c-statistic of 0.71, which shows that the prediction model is applicable to patients hospitalized in a different time period than the period of our development cohort. The calibration plots represent the agreement between the predicted and observed INR values ≥ 4.5 (Fig 1). The calibration-in-the-large was 0.34 and the calibration slope was 1.06. After correction for the calibration-in-the-large, the calibration-in-the-large was 0 and the calibration slope was 1.06.

In Fig 2 a score chart is presented which is based on the formula stated in Table 3. The score chart can be used to obtain approximate predictions for individual patients. For example, an 80 year old woman, admitted to a medical ward and treated with phenprocoumon, fluconazole and amiodarone with an ALAT of 23 U/L, LDH of 370 U/L, albumin of 40 g/L, e-GFR of 30 ml/min/1.73m^2, and a CRP of 80 mg/L. According to Fig 2, the risk of an INR ≥ 4.5 during hospital stay is 10.8% for this patient.

Table 1. Baseline characteristics of the patients included in the development and validation cohorts, number of patients (%) unless otherwise stated

Characteristic	Development 2006-2010 (n=8996)	Validation 2011-2014 (n=9018)
Male gender	5310 (59.0)	5420 (60.1)
Age, years*	72 [62.0-82.0]	69.0 [58.0-77.0]
INR ≥ 4.5 during a previous admission	868 (9.6)	813 (9.0)
VKA type, acenocoumarol	7978 (88.7)	8192 (90.8)
Ward type, medical ward	5497 (59.8)	5112 (56.7)
Use of concomitant medication		
Miconazole	153 (1.7)	82 (0.9)
Cotrimoxazole	337 (3.7)	214 (2.4)
Fluconazole	119 (1.3)	52 (0.6)
Voriconazole	7 (0.1)	27 (0.3)
Amiodarone	724 (8.0)	720 (8.0)
Rifampicin	53 (0.6)	58 (0.6)
Carbamazepine	73 (0.8)	49 (0.5)
Phenytoin	89 (1.0)	54 (0.6)
Colestyramin	17 (0.2)	89 (1.0)
Antithyroid drugs	110 (1.2)	75 (0.8)
Laboratory parameters		
ALAT (u/l)*	25.0 [16.0-44.0]	25.0 [17.0-43.0]
ASAT (u/l)*	30.0 [22.0-44.0]	31.0 [23.0-46.0]
y-GT (u/l)*	61.0 [33.0-131.0]	66.0 (32.0-144.3]
LDH (u/l)*	442.5 [357.0-589.8]	251.0 [198.0-328.0]
Albumin (g/L)*	36.0 [31.0-41.0]	37.0 [32.0-42.0]
e-GFR (ml/min/1.73m^2)*	70.0 [49.0-90.0]	68.0 [47.0-89.0]
Hb (g/l)*	116 [100-134]	116 [102-134]
TSH (mu/l)*	1.4 [0.7-2.8]	1.7 [1.0-3.0]
T3 (nmol/l)*	1.4 [1.0-1.8]	1.5 [1.4-1.9]
T4 (nmol/l)*	104.5 [83.5-132.0]	96.5 [79.5-123.5]
CRP (mg/l)*	30.0 [8.0-82.0]	23.0 [5.4-65.0]
Plt (x10^9/l)*	229.0 [175.0-300.8]	216.5 [165.0-288.0]
Leu (x10^9/l)*	8.4 [6.5-11.1]	8.7 [6.7-11.5]

*Results are presented as median [interquartile range].
ALAT (alanine amino transferase), ASAT (aspartate amino transferase), y-GT (gamma-glutamyl transferase), LDH (lactate dehydrogenase), albumin, e-GFR (estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) formula (Levey et al, 1999), Hb (hemoglobin), TSH (thyroid stimulation hormone), T3 (triiodothyronine), T4 (thyroxin), CRP (c-reactive protein), Plt (platelet count) and Leu (leucocytes).

Table 2. Associations between predictors and bleeding complications

		Odds ratio [95% CI]	
Characteristic	**Coding**	**Univariable**	**Multivariable**
Gender	Female vs male	1.29 [1.13-1.48]	1.19 [1.04-1.36]
Age, years	>60 vs ≤60	1.72 [1.50-1.97]	1.38 [1.20-1.59]
INR ≥ 4.5 during a previous admission	INR ≥ 4.5 vs INR < 4.5	1.39 [1.15-1.67]	-
VKA type	Phenprocoumon vs acenocoumarol	0.98 [0.79-1.21]	-
Ward type	Surgical ward vs medical ward	1.06 [0.93-1.21]	-
Concomitant medication			
Miconazole	Miconazole vs no miconazole	2.70 [1.82-4.00]	1.85 [1.24-2.78]
Cotrimoxazole	Cotrimoxazole vs no cotrimoxazole	2.41 [1.81-3.19]	2.20 [1.63-2.98]
Fluconazole	Fluconazole vs no fluconazole	3.55 [2.32-5.44]	2.68 [1.68-4.29]
Voriconazole	Voriconazole vs no voriconazole	17.51 [2.55-120.41]	9.36 [1.53-57.46]
Amiodarone	Amiodarone vs no amiodarone	2.23 [1.81-2.75]	2.28 [1.82-2.87]
Rifampicin	Rifampicin vs no rifampicin	2.06 [1.01-4.20]	-
Carbamazepine	Carbamazepine vs no carbamazepine	0.89 [0.42-1.90]	-
Phenytoin	Phenytoin vs no phenytoin	1.66 [0.92-2.99]	-
Colestyramin	Colestyramin vs no colestyramin	3.36 [1.07-10.60]	-
Antithyroid drugs	Antithyroid drugs vs no antithyroid drugs	2.09 [1.25-3.50]	1.80 [1.08-3.00]
Laboratory parameters			
ALAT (u/l)		0.98 [0.92-1.05]	0.93 [0.87-0.98]
ASAT (u/l)		1.05 [0.99-1.11]	-
y-GT (u/l)		1.35 [1.14-1.59]	-
LDH (u/l)		1.48 [1.29-1.69]	1.34 [1.20-1.49]
Albumin (g/l)		0.52 [0.44-0.61]	0.66 [0.55-0.78]
e-GFR (ml/min/1.73m^2)		0.69 [0.63-0.76]	0.68 [0.58-0.80]
Hb (g/l)		0.47 [0.40-0.54]	-
CRP (mg/l)		2.46 [2.08-2.91]	1.62 [1.31-2.00]
Plt (x10^9/l)		0.94 [0.82-1.07]	-
Leu (x10^9/l)		1.47 [1.32-1.64]	-

ALAT (alanine amino transferase), ASAT (aspartate amino transferase), y-GT (gamma-glutamyl transferase), LDH (lactate dehydrogenase), albumin, e-GFR (estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) formula (Levey et al, 1999), Hb (hemoglobin), CRP (c-reactive protein), Plt (platelet count) and Leu (leucocytes).

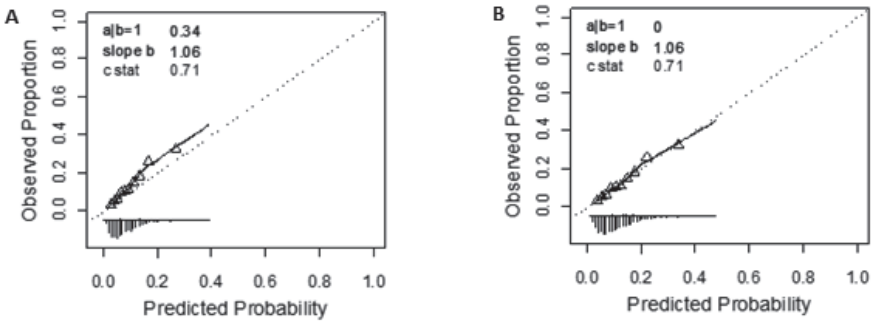

Fig 1. Validation plots for the prediction model of an INR ≥ 4.5. (A) the calibration-in-the-large was 0.34 and the calibration slope was 1.06 before correction; (B) after correction for the calibration-in-the-large, the calibration-in-the-large was 0 and the calibration slope was 1.06.The distribution of predicted risks is shown at the bottom of the graphs. Triangles indicate the observed proportions by quintiles of predicted risks

Table 3. Prediction model

Steps	Formula
1/ Calculate lp "all variables"[a]	= 0.016 x Age[b] + 0.176 x Gender[c] - 0.003 x ALAT[d] + 0.580 x log(LDH)[e] - 0.042 x Albumin[f] - 0.009 x e-GFR[g] + 0.206 x log(CRP)[h] + 0.617 x Miconazole[i] + 0.789 x Cotrimoxazole[j] + 0.987 x Fluconazole[k] + 2.237 x Voriconazole[l] + 0.826 x Amiodarone[m] + 0.587 x Antithyroid drugs[n]
2/ Calculate the lp with the intercept	= -4.282 + lp
3/ Calculate the prediction of an INR ≥ 4.5	= (1/(1+exp (-lp))) x 100%

ALAT, alanine amino transferase; CRP, C-reactive protein; e-GFR, estimated glomerular filtration rate, calculated with the modification of diet in renal disease formula (Levey et al, 1999); INR, international normalised ratio; LDH, lactate dehydrogenase.
[a]lp refers to the linear predictor in a logistic regression model.
[b]Age in years (Age equal to 0 for age ≤60 year, for age >60 year age= age-60).
[c]Gender (female=1, male=0)
[d]ALAT (alanine amino transferase) in U/L.
[e]LDH (lactate dehydrogenase) in U/L.
[f]Albumin in g/L.
[g]e-GFR (estimated glomerular filtration rate) in ml/min/1.73m^2.
[h]CRP (c-reactive protein) in mg/L.
[i]Concomitant use of miconazole (yes=1, no=0).
[j]Concomitant use of cotrimoxazole (yes=1, no=0).
[k]Concomitant use fluconazole (yes=1, no=0).
[l]Concomitant use of voriconazole (yes=1, no=0).
[m]Concomitant use of amiodarone (yes=1, no=0).
[n]Concomitant use of antithyroid drugs (yes=1, no=0).

	A	B	C
1	**Prediction of INR ≥ 4.5**		
2			
3	**Predictor**	**Coding**	**Value**
4	Age*	years	20
5	Gender	0=male, 1=female	1
6	ALAT (U/L)		23
7	LDH (U/L)		370
8	Albumin (g/L)		40
9	e-GFR (ml/min/1.73m^2)		30
10	CRP (mg/L)		80
11	Miconazole	0=no, 1=yes	0
12	Cotrimoxazole	0=no, 1=yes	0
13	Fluconazole	0=no, 1=yes	1
14	Voriconazole	0=no, 1=yes	0
15	Amiodarone	0=no, 1=yes	1
16	Antithyroid drugs	0=no, 1=yes	0
17			
18	**Risk of INR ≥ 4.5**		**10.8%**

Fig 2. Screenshot of the spreadsheet with calculations for an individual patient using the prediction model. [a]Age (=0, for age ≤60 years; =age (in years) – 60, for age >60 years). ALAT, alanine amino transferase; CRP, C-reactive protein; e-GFR, estimated glomerular filtration rate, calculated with the modification of diet in renal disease formula (Levey et al, 1999); INR, international n ormalised ratio; LDH, lactate dehydrogenase

DISCUSSION

We developed and validated a clinical prediction model for an INR ≥ 4.5 in patients admitted to medical or surgical wards who are treated with VKAs. The prediction model can help physicians to identify patients at the lower spectrum of thromboembolic risk and for whom the risk of bleeding during VKA therapy is high. Using the prediction model may also help in counseling and informing patients about their potential risk for hemorrhage while on anticoagulants, and in identifying patients who might benefit from more careful management of anticoagulation.

To our knowledge, this is the first study to develop such a clinical prediction model. The strongest predictors for an INR ≥ 4.5 during hospitalization were concomitant use of voriconazole, fluconazole, amiodarone, cotrimoxazole or miconazole. These drugs inhibit the metabolism of VKAs by inhibiting the liver enzyme CYP2C9 (Cadiou *et al*, 2008; Harder *et al*, 1996), and thus, an increased risk of an INR ≥ 4.5 is expected.

Concomitant use of rifampicin, carbamazepine, phenytoin or colestyramin showed no association of the occurrence of an INR ≥ 4.5. These medications induce the metabolism of VKAs by inducing the liver enzyme CYP2C9, and thus, a decreased risk of an INR ≥ 4.5 was expected. We assumed to find a similar effect of antithyroid drugs, which also induce the metabolism of VKAs leading to a decrease of an INR ≥ 4.5. However, our study showed an increased risk of an INR ≥ 4.5 when antithyroid drugs were used concomitantly. We have no explanation for this.

In our study we found that women had a 1.2 fold (95% CI, 1.1-1.4) higher risk of an INR ≥ 4.5 than men. Our results are in line with prior studies that found an increased frequency of bleeding among women treated with vitamin K antagonists. Cosma Rochat et al. found that hospitalized women receiving vitamin K antagonists had a 4-fold increased risk of bleeding compared with men. A possible explanation for the higher bleeding risk in women may be a systematic sex difference in the coagulation and fibrinolytic cascades (Cosma Rochat *et al*, 2009; Reynolds *et al*, 2007).

Furthermore, advanced age was associated with an increased risk of an INR ≥ 4.5, a finding that is consistent with previous studies (Kuijer *et al*, 1999; Gage *et al*, 2006; Pisters *et al*, 2010; Torn *et al*, 2005). The predictors type of ward and type of VKA showed no relation with INR ≥ 4.5 in this study. Gadisseur et al found that the short acting acenocoumarol is associated with more variability in INR (Gadisseur *et al*, 2002), but in our study, this does not lead to a higher risk of overanticoagulation compared to phenprocoumon.

The risk profile and metabolism of warfarin, which is the main VKA used in other countries, is generally similar to that of acenocoumarol and phenprocoumon (Ufer et al, 2005; Beinema *et al*, 2008). These VKAs differ in elimination half-life and response to polymorphisms in the gene coding for the metabolizing enzyme CYP2C9. Acenocoumarol has the shortest half-life (8-14 hour) and greatest response to polymorphisms. Phenprocoumon has the longest elimination half-life (120-200 hour) and lowest response. The half-life of warfarin ranges from 20-60 hours, with a mean of about 40 hours (Ufer et al, 2005; Beinema *et al*, 2008).

In several other models, an INR ≥ 4.5 during a previous hospital admission was included in the final model (Beyth *et al*, 1998; Kuijer *et al*, 1999; Gage *et al*, 2006; Pisters *et al*, 2010; Fang *et al*, 2011), but this was not confirmed in our study. A reason for this may be that two subsequent hospitalizations are totally different (i.e. type of ward, concomitant medication, reason for hospitalization) and too far apart with the result that both hospitalization cannot be compared to each other.

Elevated liver enzymes (ALAT, ASAT, γ-GT and LDH) may indicate inflammation or damage to cells in the liver. The observed association in this study of an increased LDH with an increased risk of an INR ≥ 4.5 could be the result of a deteriorating capacity of the liver to produce clotting factors or to metabolize VKAs properly. The same association was expected between ALAT, ASAT, γ-GT and INR ≥ 4.5. However, patients with an elevated ALAT level had a lower risk of an INR ≥ 4.5 and ASAT and γ-GT showed no relation with INR ≥ 4.5 in this study. As shown in Table II, the observed ALAT and ASAT levels in our population were not very high. This may be the reason that our findings are in contradiction with what we expected.

Higher concentrations of albumin were predictive for a decrease in risk of an INR ≥ 4.5. VKAs bind to albumin in plasma and only unbound drugs have a pharmacological effect. Another possible explanation is that lower concentrations of albumin represents a deteriorating condition of the patient resulting in a reduced intake of vitamin K.

Patients with a high e-GFR have a 0.7 fold (95% CI, 0.6-0.8) lower risk of an INR ≥ 4.5 than patients with a low renal function. However, the elimination of VKAs does not depend on the renal function so a causal link cannot be established. VKAs are mainly metabolized by liver enzymes to inactive metabolites that are excreted in the urine. The positive effect of a good renal function may be the result of a better condition of the patient in general.

Our results also showed that high CRP levels were predictive for an increased risk of an INR ≥ 4.5. CRP has a positive association with infections and inflammations which might affect coagulation. A potential mechanism for the higher risk of an INR ≥ 4.5 during infections and inflammations is the increased catabolism of vitamin K dependent clotting factors and inhibition of VKA metabolism (Timothy *et al*, 2015).

Most models that have been developed by others use binary values for age groups, liver and renal disease (Kuijer *et al*, 1999; Gage *et al*, 2006; Pisters *et al*, 2010; Fang *et al*, 2011; Beyth *et al*, 2002). Our final prediction model consists of predictors with continuous values for age and for laboratory values. This makes it difficult to compare our model to other models. The predictors age (Beyth *et al*, 1998; Kuijer *et al*, 1999; Gage *et al*, 2006; Ruiz-Gimenez *et al*, 2008; Pisters *et al*, 2010; Fang *et al*, 2011) and renal function (Beyth *et al*, 1998; Kuijer *et al*, 1999; Gage *et al*, 2006; Ruiz-Gimenez *et al*, 2008; Pisters *et al*, 2010; Fang *et al*, 2011) seem to be present in most models. Our model includes several concomitant medications that are easily extractable from the EMR.

Limitations

The first limitation is that we used a surrogate marker for an increased risk of bleeding. We would have preferred to predict bleeding itself, but that complication was not registered in an easily extractable way in the EMR. An INR ≥ 4.5 is an adequate marker because 4.5 is the level at which the risk of bleeding increases sharply (Palareti et al, 1996; Amouyel et al, 2009; Hylek et al, 2003). Second, although we had many candidate predictors, several potentially significant predictors were not available. For example, information on the indication for VKA treatment or on the target INR was lacking. Patients with a mechanical heart valve, for example, have a higher target INR (2.5-3.5) than patients with atrial fibrillation, where the target INR ranges from 2.0 to 3.0 (ESC guidelines for Atrial fibrillation, 2016). Patients with a higher target INR are therefore more susceptible to reach a supratherapeutic INR (Meschengieser *et al*, 1997). We couldn't include comorbidities, since they were not extractable from the EMR. Furthermore, this study has included all adult patients admitted to the hospital, except those admitted to the ICU. This might introduce selection bias because patients who have been transferred to the ICU represent a special group of patients with increased disease severity that is not represented in this study. Finally, the study was performed in one university hospital which may limit generalizability.

Strengths

Notwithstanding these limitations, the strong point of our study is that we included all adult patients admitted to medical or surgical wards of the hospital. Another strength is that we validated our model, which showed that the prediction model is applicable to patients hospitalized in a different time period than in our development cohort. Furthermore, the predictors in the model are extracted from the EMR, which makes it possible to develop an electronic prediction rule, enabling doctors to make easy assessments about individual risks of an INR ≥ 4.5.

Implications

This study shows that it is possible to develop an electronic prediction rule for an INR ≥ 4.5 in hospitalized patients using vitamin K antagonists. The prediction model can help physicians to identify patients at the lower spectrum of thromboembolic risk and for whom the risk of bleeding during VKA therapy is high. Using the prediction model may also help in counseling and informing patients about their potential risk for hemorrhage while on anticoagulants, and in identifying patients who might benefit from more careful management of anticoagulation. Alternatively, these patients can also be switched to the direct oral anticoagulants (DOACs) which cause less major bleeding, such as intracranial hemorrhages, compared to VKAs (Adam *et al*, 2012).

The methodology for developing an electronic prediction rule for VKAs used in our study, may also be applied to other anticoagulants, such as the DOACs. Future studies are necessary to further improve the prediction model by including patients admitted to the ICU, and by incorporating time in the therapeutic range (TTR) which is associated with the effectiveness and safety of VKA therapy (Lin *et al*, 2017).

Furthermore, information about the indication of the VKA, the duration of use of VKAs before admission and comorbidities can be included to the prediction model to investigate whether it leads to a more accurate prediction model. Ideally, a prospective intervention study should be performed after implementation of the electronic prediction rule, to investigate whether the use of such a rule leads to a decrease in the number of admissions during which an INR ≥ 4.5 occurs and whether this results in less bleeding complications.

CONCLUSIONS

We developed a clinical prediction rule with a *c*-statistic of 0.71 for an INR ≥ 4.5 in patients admitted to medical or surgical wards who are treated with VKAs. The model includes several risk factors, including concomitant medication, which are easily extractable from electronic patient records. This enables the creation of a clinical decision support rule, based on the prediction model identified in this study.

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Supplementary Table 1. Data collection

Part	Data content
Patient data	Patient ID
	Date of birth
	Gender
	Date of hospitalization
	Date of hospital discharge
	Deceased (yes/no)
	If deceased , date of death
	Type of ward (surgical/medical)*
Medication data	Type of VKA (phenprocoumon/acenocoumarol)
	Date of start of VKA
	Date of end of VKA
	Concomitant medication that increase the effect of VKAs:
	• Miconazole, cotrimoxazole, fluconazole, voriconazole and amiodarone
	Concomitant medication that decrease the effect of VKAs:
	• Rifampicin, carbamazepine, phenytoin, colestyramin and antithyroid drugs
Clinical chemistry data	Laboratory values:
	INR
	ALAT (u/l)
	ASAT (u/l)
	y-GT (u/l)
	LDH (u/l)
	Albumin (g/L)
	Hb (g/l)
	Creatinine
	e-GFR (ml/min/1.73m^2)
	TSH (mU/l)
	T3 (nmol/l)
	T4 (nmol/l)
	CRP (mg/l)
	Plt (x10^9/l)
	Leu (x10^9/l)
Study outcome	INR ≥ 4.5 during VKA exposure and date of determination

*The cardiology wards, internal medicine wards, oncology wards and psychiatry wards were classified as 'medical', and the surgical wards, ear-nose-throat and eye surgery wards were classified as 'surgical'.
ALAT (alanine amino transferase), ASAT (aspartate amino transferase), y-GT (gamma-glutamyl transferase), LDH (lactate dehydrogenase), albumin, Hb (hemoglobin), creatinine, e-GFR (estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) formula (Levey et al, 1999), TSH (thyroid stimulation hormone), T3 (triiodothyronine), T4 (thyroxin), CRP (c-reactive protein), Plt (platelet counts) and Leu (leucocytes).

Supplementary Table 2. The variables for which laboratory values were missing

	Number missing (%)		
Variable	**Total (n=8996)**	**INR ≥ 4.5 (n=1507)**	**INR < 4.5 (n=7489)**
ALAT (u/l)	6927 (77)	1066 (71)	5861 (78)
ASAT (u/l)	6922 (77)	1064 (71)	5858 (78)
y-GT (u/l)	7081 (79)	1093 (73)	5988 (80)
LDH (u/l)	6756 (75)	1025 (68)	5731 (77)
Albumin (g/l)	7653 (85)	1196 (79)	6457 (86)
e-GFR (ml/min/1.73m^2)	5132 (57)	781 (52)	4351 (58)
Hb (g/l)	4910 (55)	750 (50)	4160 (56)
CRP (mg/l)	6066 (67)	874 (58)	5192 (69)
Plt (x 10^9/)	6316 (70)	986 (65)	5330 (71)
Leu (x 10^9/l)	5735 (64)	854 (57)	4881 (65)
T3 (nmol/l)	8953 (99)	1497 (99)	7456 (99)
T4 (nmol/l)	8946 (99)	1499 (99)	7447 (99)
TSH (mU/l)	8707 (97)	1455 (97)	7252 (97)

ALAT (alanine amino transferase), ASAT (aspartate amino transferase), y-GT (gamma-glutamyl transferase), LDH (lactate dehydrogenase), albumin, e-GFR (estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) formula (Levey et al, 1999), Hb (hemoglobin), CRP (c-reactive protein), Plt (platelet counts) and Leu (leucocytes), T3 (triiodothyronine), T4 (thyroxin) and TSH (thyroid stimulation hormone).

Chapter 3

Risk of bleeding in hospitalized patients on anticoagulant therapy: Prevalence and potential risk factors

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ABSTRACT

Introduction

Bleeding is the most important complication of treatment with anticoagulant therapy. Although several studies have identified risk factors of bleeding in outpatients, no studies have been performed that evaluated prevalence and potential risk factors of bleeding in hospitalized patients treated with anticoagulant therapy.

Methods

The primary objective of this study was to determine the prevalence of bleeding in anticoagulant users during hospitalization. The secondary objective was to identify potential risk factors of bleeding in hospitalized patients on anticoagulant therapy. A prospective, observational cohort study was conducted in two Dutch hospitals. Adult patients hospitalized between October 2015 and October 2016 treated with anticoagulant therapy were included. Bleeding was defined as a composite endpoint of major bleeding and non-major bleeding according to the International Society on Thrombosis and Heamostasis (ISTH) criteria. Data analysis was performed by multivariate logistic regression.

Results

The prevalence of in-hospital bleeding in patients using anticoagulant therapy was 7.2%; 95% confidence interval [95% CI] 5.5-9.1 (65 out of 906 patients). Multivariate logistic regression analysis indicated that female gender (adjusted odds ratio [ORadj] 2.1; 95% CI 1.2-3.7), high-bleeding-risk surgical procedure (ORadj 5.3; 95% CI 2.7-10.2), low-bleeding-risk surgical procedure (ORadj 4.9; 95% CI 1.9-12.6), and non-surgical interventions (ORadj 6.2; 95% CI 3.0-12.6) were associated with bleeding events in hospitalized patients treated with anticoagulants.

Conclusions

The prevalence of bleeding in anticoagulant users during hospitalization was 7.2%. This study detected potential risk factors that can help to identify patients on anticoagulants who have an increased risk of bleeding during hospitalization.

INTRODUCTION

Anticoagulants are frequently used medications in the prevention and treatment of thromboembolic disease [1,2]. Despite the clinical benefits, bleeding is the most important complication of treatment with anticoagulants [1,3]. In the Netherlands, the HARM (Hospital Admissions Related to Medication) study showed that 5.6% of all unplanned hospitalizations were drug-related and that 6.3% of these drug-related hospitalizations were attributable to the use of anticoagulants and 8.7% to antiplatelet drugs [4].

Various studies have identified risk factors of bleeding in patients treated with anticoagulants. Shoeb et al. and Fitzmaurice et al. reported that increasing age and female gender are associated with increased risk of bleeding [5,6]. Other risk factors of bleeding were comorbidities (such as cancer, hypertension, diabetes, renal impairment, anemia, bleeding in history, and genetic polymorphism) and concomitant use of interacting drugs [7-12].

Most published studies focused on risk factors of bleeding in outpatients treated with vitamin K antagonists (VKAs) for specific indications, such as atrial fibrillation (AF) or venous thromboembolism (VTE) [7-11]. However, little is known about the potential risk factors of bleeding in hospitalized patients treated with anticoagulants. Compared to outpatients, hospitalized patients may be at increased risk of bleeding, for example because of perioperative bridging of anticoagulation therapy and start of additional medication influencing the metabolism of anticoagulants [13,14]. Furthermore, most studies identified risk factors of bleeding in patients treated with VKAs and did not include patients using direct oral anticoagulants (DOACs) [7-11].

The primary aim of this study was to determine the prevalence of bleeding in anticoagulant users during hospitalization. Secondary goal was to identify potential risk factors of bleeding in hospitalized patients treated with anticoagulant therapy.

METHODS

Study design

The design of this study is a prospective, observational multicenter cohort study. This study is part of a larger antithrombotic stewardship study (S-team study), in which the effect of a multidisciplinary antithrombotic team on the safety and efficacy regarding antithrombotic therapy during hospitalization is studied using a pre-post study design

[15]. We aim to include 1900 patients, 950 patients in the pre-implementation phase and 950 patients in the post-implementation phase of the S-team study. For this study all patients from the pre-implementation phase of the S-team study were enrolled. The S-team study was approved by the Medical Ethics Committee of the Erasmus University Medical Center (MEC-2015-386).

Study setting

The study is conducted in the Erasmus University Medical Center (EMC) and the Reinier de Graaf Hospital (RdGG). The EMC is a 1320-bed University Medical Center based in Rotterdam, the Netherlands. The RdGG is a general teaching hospital located in Delft, the Netherlands, with 590 beds.

Study population

Patients aged 18 years and older who were admitted to the EMC and RdGG between October 2015 and October 2016 and treated with anticoagulant therapy were eligible for inclusion. The study population consisted of patients who started with anticoagulant therapy in the hospital, patients who were already treated with anticoagulant therapy before hospitalization and patients who restarted anticoagulant therapy after a surgical or non-surgical intervention. Owing to the limited availability of study personnel, we recruited three patients per day per hospital. A random number generator was used to select those three patients. Only the patient's first hospital admission was included. All participants provided informed consent during hospitalization. Exclusion criteria were the following: (1) no informed consent from the patient, (2) hospitalization for less than 24 hours, (3) admission to the intensive care unit (ICU) without admission to a general care ward, (4) patients treated with low-molecular-weight-heparins (LMWHs) only as thrombosis prophylaxis, (5) patients started with acenocoumarol three days or less, phenprocoumon five days or less, or DOACs one day or less prior to hospital discharge were excluded for analysis.

Data collection

The hospital information system was used for data collection (Table S1). Patient data were coded according to Dutch privacy guidelines. Data were collected during hospital stay from the day of hospitalization or time of establishing the first anticoagulant therapy or from the day of discharge of the ICU to a general care ward until discharge from hospital or patient death. In patients who were initially admitted to a general care ward and subsequently transferred to the ICU, data were collected from the day of hospitalization until admission to the ICU.

Potential risk factors

The following potential risk factors, based on identified risk factors of bleeding in outpatients, were included in the analysis: gender, age, bleeding in history (yes/no), cancer (yes/no), hospital type (University Medical Center vs general teaching hospital), bleeding risk of the surgical procedure (high, low, and clinically non-relevant bleeding risk) [17,18], non-surgical interventions (endoscopic interventions and endovascular coiling) (yes/no), estimated glomerular filtration rate (e-GFR) on the day of hospitalization, type of anticoagulant therapy and concomitant use of known interacting drugs.

We defined concomitant use of known interacting drugs as an active prescription at the same time the VKA or DOAC was prescribed. The following drugs were considered as interacting drugs that increase the effect of VKAs the most; miconazole, cotrimoxazole, fluconazole, voriconazole and amiodarone [19]. Ketoconazole, itraconazole, voriconazole, cyclosporine, tacrolimus and verapamil were considered to increase the effect of DOACs the most [19]. The interacting drugs with VKAs and DOACs were clustered for the analysis into two groups; VKA interacting drugs and DOAC interacting drugs.

Outcome

Primary outcome was the prevalence of bleeding in anticoagulant users during hospitalization. Patients with bleeding as a reason for admission were also eligible for inclusion; however those bleeding events were not included in the primary endpoint. Bleeding was defined as a composite endpoint of major bleeding and non-major bleeding according to the International Society on Thrombosis and Heamostasis (ISTH) criteria (Table 1) [20,21]. Because our study started in 2015 we did not use the most recent ISTH classification of bleeding. The bleeding events were evaluated and classified according to the ISTH criteria by two independent expert physicians in the field (FNC and EK). In patients where more than one bleeding event was observed during hospitalization, only the first bleeding event was included. Secondary outcome was the potential risk factors that are associated with bleeding in hospitalized patients on anticoagulant therapy.

Sample size

Annual bleeding (major and non-major) rates are 2-3% depending on the type of anticoagulant, but in every day practice it seems that this rate is at least 10% [22-24]. Based on the number of potential risk factors included in the analysis (nine potential risk factors) and the assumption that ten cases are needed for every predictor studied [25], the required sample size will be 900 patients. In order to account for drop-outs, 950 patients will be included.

Table 1. ISTH definitions of bleeding in patients

Type of bleeding	Definition of bleeding
Major bleeding in non-surgical patients [Schulman 2005]	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)
Major bleeding in surgical patients [Schulman 2010]	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

Data analysis

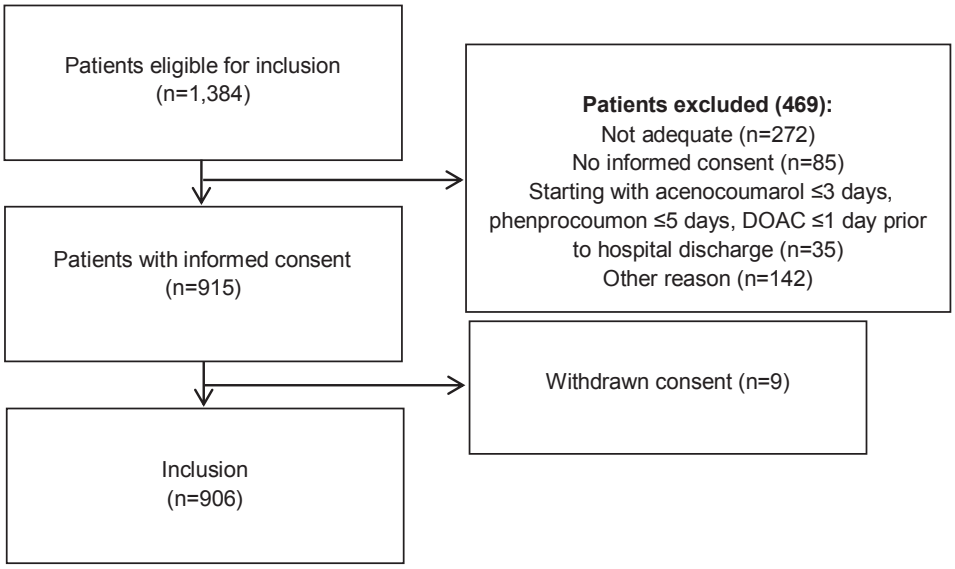
All data were processed with Open Clinica® and analyzed with SPSS version 21.0. Descriptive statistics were used to determine the prevalence of bleeding in anticoagulant users during hospitalization. Univariate logistic regression analysis was performed to identify potential risk factors of bleeding during hospitalization. Potential risk factors that showed a significant association ($p < 0.1$) in the univariate analysis were entered in a multivariate model, using a stepwise enter method. Variables that changed the beta-coefficient with more than 10% were retained in the model. Adjusted odds ratio's (ORadj) and 95% confidence intervals (95% CI) were reported.

We planned to perform a sensitivity analysis for the potential risk factor, VKA interacting drugs, including only patients who used VKAs.

RESULTS

Study population

During the study period 1,384 patients were eligible for inclusion. In 469 patients, at least one reason for exclusion was present. Nine patients withdrew their consent after signing the informed consent. In total 906 patients were included in our analysis (Figure 1). Characteristics of the included patients are presented in Table 2. Of these, 544 (60%) were male, median age was 70 (range 59-78) years and 323 (35.7%) patients had surgery. The most frequently performed surgical procedures were cardio-thoracic (27.2%), vascular (24.5%) and trauma and orthopedic (13.9%). Admission for medical reasons occurred in 583 (64.3%) patients. We included 365 (40.3%) patients who were admitted through the emergency department. Median length of stay in all patients was 8 days with a range of 5 to 14 days. The median length of stay in patients with a bleeding during hospitalization was 18 days (range of 8.5 to 34.5 days), and 7 days (range of 4 to 13 days) in patients without a bleeding during hospitalization.



DOAC Direct Oral Anticoagulant

Figure 1. Study flow

Table 2. Baseline characteristics of the patients

Characteristic	All patients (*n*=906)	Patients with bleeding during hospitalization (*n*=65)	Patients without bleeding during hospitalization (*n*=841)
Male gender	544 (60)	31 (47.7)	513 (61)
Age, years	70 [59-78]	70 [57.5-79]	70 [59-78]
Length of hospitalization, days	8 [5-14]	18 [8.5-34.5]	7 [4-13]
Prior bleeding	194 (21.4)	11 (16.9)	183 (21.8)
Thrombocytopenia	8 (0.9)	2 (3.1)	6 (0.7)
Cancer	221 (24.4)	18 (27.7)	203 (24.1)
Hospital type, University Medical Center	454 (50.1)	45 (69.2)	409 (48.6)
Surgery			
High bleeding risk procedure	227 (25.1)	34 (52.3)	193 (22.9)
Low bleeding risk procedure	57 (6.3)	8 (12.3)	49 (5.8)
Clinically non-relevant bleeding risk procedure	39 (4.3)	3 (4.6)	36 (4.3)
Non-surgical interventions	80 (8.8)	16 (24.6)	64 (7.6)
e-GFR, ≤50 ml/min/1.73m^2	293 (32.3)	21 (32.3)	272 (32.3)
Type of anticoagulant therapy			
VKA monotherapy	289 (31.9)	11 (16.9)	278 (33.1)
DOAC monotherapy	54 (6.0)	3 (4.6)	51 (6.1)
LMWH monotherapy	139 (15.3)	14 (21.5)	125 (14.9)
VKA + LMWH	196 (21.6)	19 (29.2)	177 (21.0)
Combination of SAPT with a VKA or DOAC or LMWH	144 (15.9)	14 (21.5)	130 (15.5)
Combination of DAPT with a VKA or DOAC or LMWH	84 (9.3)	4 (6.2)	80 (9.5)
VKA interacting drugs	124 (13.7)	12 (18.5)	112 (13.3)

Results are presented as median [interquartile range] or as number of patients (%) for non-continues data. N, number of patients at risk; e-GFR, estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) formula [16]; VKA, vitamin-K antagonist; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight-heparin; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy.

The most frequently used anticoagulants were VKA monotherapy (31.9%) and simultaneous use of VKA and LMWH because of perioperative bridging therapy (21.6%). Of the 668 VKA and DOAC users in our study, 75 (11.2%) patients were prescribed a VKA or DOAC for the first time.

Table 3. Type and dose of antiplatelet drug in addition to treatment with VKAs or DOACs

Type and dose of antiplatelet drug in combination with a VKA or DOAC	All users (*n*=158)
Combination of a VKA with SAPT	**125 (79.1)**
Acetylsalicylic acid 80 mg once daily	50 (31.6)
Calcium carbasalate 100 mg once daily	17 (10.8)
Clopidogrel 75 mg once daily	55 (34.8)
Prasugrel 5 mg once daily	1 (0.6)
Ticagrelor 90 mg twice daily	2 (1.3)
Combination of a VKA with DAPT	**23 (14.6)**
Acetylsalicylic acid 80 mg once daily + Clopidogrel 75 mg once daily	10 (6.3)
Calcium carbasalate 100 mg once daily + Clopidogrel 75 mg once daily	5 (3.2)
Calcium carbasalate 100 mg once daily + Ticagrelor 90 mg twice daily	8 (5.1)
Combination a DOAC with SAPT	**8 (5.1)**
Dabigatran 110 mg twice daily + Acetylsalicylic acid 80 mg once daily	1 (0.6)
Dabigatran 110 mg twice daily + Calcium carbasalate 100 mg once daily	3 (1.9)
Dabigatran 110 mg twice daily + Clopidogrel 75 mg once daily	3 (1.9)
Rivaroxaban 15 mg once daily + Acetylsalicylic acid 80 mg once daily	1 (0.6)
Combination of a DOAC with DAPT	**2 (1.2)**
Apixaban 5 mg twice daily + Calcium carbasalate 100 mg once daily + Clopidogrel 75 mg once daily	1 (0.6)
Dabigatran 110 mg twice daily + Calcium carbasalate 100 mg once daily + Clopidogrel 75 mg once daily	1 (0.6)

N, number of patients at risk; VKA, vitamin-K antagonist; DOAC, direct oral anticoagulant; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy.

Combination of anti-platelet therapy with VKAs or DOACs occurred in 158 patients. Detailed information on type and dose of the received antiplatelet drugs are listed in Table 3.

The majority of enrolled patients received anticoagulant therapy for the treatment of venous thromboembolism (48.2%), atrial fibrillation (42.9%), cardiac valve surgery (3.2%) and other reasons (5.7%). VKA interacting drugs were used in 124 (13.7%) patients. Due to the low number of DOAC users during our study period we found no concomitant use of interacting drugs with DOACs.

Characteristics of all bleeding events

The prevalence of all in-hospital bleeding in patients using anticoagulant therapy was 7.2%; 95% CI 5.5-9.1 (65 out of 906 patients). Seven patients had two bleeding events during hospitalization and in two patients three bleeding events occurred during hospitalization. Two patients that were admitted because of a bleeding developed a new bleeding event during hospitalization. Of the 65 patients with a bleeding, 51 (78.5%) were categorized as major bleeding and 14 (21.5%) as non-major bleeding. The most common sites of bleeding were surgical site bleeding (n = 47, 72.3%), followed by gastrointestinal bleeding (n = 9, 13.8%) and urogenital bleeding (n = 4, 6.1%). One out of seventy seven endoscopic interventions was complicated by bleeding. Of the 65 bleeding events, one contributed to death, 48 were associated with a fall in hemoglobin level of ≥ 20 g/L (1.24 mmol/l), and 39 led to a transfusion of two or more units of whole blood or red cells. In 44 patients on VKA therapy, four patients had an International normalized ratio (INR) of >3.5 at the time of bleeding. Five patients had an INR between 2-3, and an INR of <2 was noticed in 32 patients at the time of bleeding. In three patients the INR was unknown. Four patients were treated with DOACs at the time of bleeding. The DOACs were correctly dosed in all four patients.

Bleeding in non-surgical patients

The prevalence of in-hospital bleeding in non-surgical patients using anticoagulant therapy was 2.2% (13 out of 583 patients); 7 (53.8%) patients with major and 6 (46.2%) patients with non-major bleeding. The most common sites of bleeding were gastrointestinal bleeding (n = 5, 38.5%) and urogenital bleeding (n = 4, 30.8%). Of the 13 bleeding events, 7 were associated with a fall in hemoglobin level of ≥ 20 g/L (1.24 mmol/l), and 5 led to a transfusion of two or more units of whole blood or red cells.

Bleeding in surgical patients

In-hospital bleeding occurred in 52 out of 323 (16.1%) surgical patients. All patients with surgical-associated bleeding were on active anticoagulation when the bleeding occurred. Major bleeding occurred in 44 (84.6%) patients, non-major bleeding in 8 (15.4%) patients. Surgical site bleeding was the most frequent site of bleeding (n = 47, 90.4%). Forty-one bleeding events were associated with a fall in hemoglobin level of ≥ 20 g/L (1.24 mmol/l), and 34 led to a transfusion of two or more units of whole blood or red cells.

Table 4. Potential risk factors of any bleeding in hospitalized patients on anticoagulant therapies after univariate logistic regression (odds ratio) and multivariate logistic regression (adjusted odds ratio)

Potential determinant	OR [95% CI]	ORadj [95% CI]
Female gender	**1.7 [1.0-2.8]**	**2.1 [1.2-3.7]**
Age, years	1.0 [1.0-1.0]	-
Bleeding in history	0.7 [0.4-1.4]	-
Cancer	1.2 [0.7-2.1]	-
Hospital type		
General teaching hospital	Ref.	
University Medical Center	**2.4 [1.4-4.1]**	1.3 [0.7-2.4]
Surgery		
No surgery	Ref.	
High bleeding risk procedure	**4.9 [2.8-8.8]**	**5.3 [2.7-10.2]**
Low bleeding risk procedure	**4.6 [1.9-11.0]**	**4.9 [1.9-12.6]**
Clinically non-relevant bleeding risk procedure	**2.3 [0.7-8.3]**	1.9 [0.5-7.0]
Interventions		
No non-surgical interventions	Ref.	
Non-surgical interventions	**4.0 [2.1-7.4]**	**6.2 [3.0-12.6]**
e-GFR		
>50 ml/min/1.73m2	Ref.	
≤ 50 ml/min/1.73m2	1.0 [0.6-1.7]	-
Type of anticoagulant therapy		
VKA monotherapy	Ref.	
DOAC monotherapy	1.5 [0.4-5.5]	-
LMWH monotherapy	**2.8 [1.3-6.4]**	2.0 [0.8-5.0]
VKA + LMWH	**2.7 [1.3-5.8]**	1.8 [0.8-4.1]
Combination of SAPT with a VKA or DOAC or LMWH	**2.7 [1.2-6.3]**	2.1 [0.9-4.9]
Combination of DAPT with a VKA or DOAC or LMWH	1.3 [0.4-4.1]	-
Interacting drugs		
No VKA interacting drugs	Ref.	
VKA interacting drugs	1.5 [0.8-2.8]	-
Sensitivity analysis VKA interacting drugs	**1.9 [1.0-3.6]**	1.5 [0.7-3.2]

Numbers in bold are statistically significant. OR, odds ratio; 95%CI, 95% confidence interval; ORadj, adjusted odds ratio; e-GFR, estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) formula [16]; VKA, vitamin-K antagonist; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight-heparin; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy

Potential risk factors of bleeding

Details of the univariate and multivariate logistic regression analysis to identify potential risk factors of any bleeding in hospitalized patients treated with anticoagulants are presented in Table 4. After multivariate analysis, the following variables were identified as predictors for any bleeding: female gender (ORadj 2.1; 95% CI 1.2-3.7), high-bleeding-risk surgical procedure (ORadj 5.3; 95% CI 2.7-10.2), low-bleeding-risk surgical procedure (ORadj 4.9; 95% CI 1.9-12.6), and non-surgical interventions (ORadj 6.2; 95% CI 3.0-12.6). The sensitivity analysis for the VKA interacting drugs predictor, including only patients who have used VKAs, showed no increased risk of bleeding in the multivariate analysis. Stratified analysis for major bleeding events showed similar predictors (Table S2).

DISCUSSION

In our study, we found that the prevalence of in-hospital bleeding events in patients using anticoagulant therapy was 7.2%; 95% CI 5.5-9.1 in all patients (65 out of 906 patients), and as high as 16.1% in surgical patients. Of all bleeding events, 78.5% were major bleeding events and 21.5% non-major bleeding events. Female gender, high-bleeding-risk surgical procedure, low-bleeding-risk surgical procedure and non-surgical interventions were associated with bleeding in hospitalized patients treated with anticoagulants.

The prevalence of bleeding observed in our inpatient population is higher than reported in a previous study in outpatients [26]. Linkins et al. evaluated VKA-related bleeding complications in patients who received oral anticoagulant therapy for at least 3 months. The authors analyzed thirty-three studies in this meta-analysis and included 10.757 patients who received anticoagulant therapy. The prevalence of major bleeding events was 2.6% (276 out of 10.757 patients). An explanation for the larger number of bleeding events in our population is that hospitalized patients are more vulnerable compared to outpatients due to start of additional medication influencing the metabolism of anticoagulants and because of (surgical) interventions. This is confirmed by the finding that the majority of bleeding events in our study occurred in surgical patients (16.1%), in comparison with non-surgical patients (2.2%).

Female gender was associated with bleeding in hospitalized patients treated with anticoagulants and is recognized before as risk factor of bleeding [27,28]. Cosma Rochat et al. found that after adjustment for patient characteristics (e.g. age), hospitalized women receiving oral anticoagulant therapy experienced a 4-fold increased risk of bleeding compared with men [27]. Patients who underwent a surgical procedure (high

or low-bleeding-risk procedures) were more at risk of having a bleeding compared to patients who had no surgery. The management of bridging anticoagulation therapy in patients undergoing high and low-bleeding-risk surgical procedures is a complex process which could be an explanation of the increased risk of bleeding in surgical patients [14]. We found no increased risk of bleeding in patients who underwent a clinically non-relevant bleeding risk surgical procedure. Contrary to high and low-bleeding-risk surgical procedures, anticoagulant therapy can be continued in the perioperative period during clinically non-relevant bleeding risk procedures [14].

Non-surgical interventions were also associated with an increased risk of bleeding. A potential explanation for this increased risk of bleeding is confounding. An endoscopic intervention for example is important for the diagnosis and primary treatment of bleeding and is therefore used because of a bleeding event. This was confirmed by our results, because only one bleeding event occurred as a result of an endoscopic intervention.

The present study showed no association of combined VKA and LMWH treatment and the risk of bleeding. Because combined treatment is often used for a short period (e.g. postoperative), it is relatively safe for these patients [29].

Combination of single antiplatelet therapy (SAPT) with a VKA or DOAC or LMWH and combination of dual antiplatelet therapy (DAPT) with a VKA or DOAC or LMWH showed no increase of bleeding risk compared to patients using VKA monotherapy. This can be explained by the fact that antiplatelet therapy co-administered with anticoagulants most likely were prescribed to patients considered at decreased risk of bleeding.

Furthermore, we found no significant difference in bleeding between patients using DOAC monotherapy and patients using VKA monotherapy. The use of DOACs was substantially less than VKAs in the Netherlands at the time of our study [30], which could be a possible reason for not finding a significant difference between DOAC and VKA users.

Several commonly cited risk factors of bleeding, such as advanced age [7,9,31,32] and prior bleeding [7,9,10] showed no association with an increased risk of bleeding in our study. These findings are consistent with Rochat et al., who attribute this to the uncertainty of their effect on the short-term risk of bleeding. The mean follow-up duration of eight days in our study confirmed that factors, such as advanced age and prior bleeding may not have a major impact on short-term bleeding risk [27].

We found no increased risk of bleeding in patients using concomitant interacting drugs with VKAs. These drugs inhibit the metabolism of VKAs by inhibiting the liver enzyme CYP2C9 and therefore an increased risk of bleeding was expected [33,34].

Furthermore, we expected to find more bleeding events in patients admitted to a University Medical Center compared to a general teaching hospital since patients may be transferred to a University Medical Center because of a high medical complexity, which may be accompanied by a high risk of bleeding. However, we found no difference in the prevalence of bleeding events between the two types of hospitals.

Stratified analysis for major bleeding events showed the same potential risk factors compared to the risk factors for any bleeding. This confirms the association with the identified risk factors.

Strengths and limitations

This study is the first study on the prevalence and potential risk factors of bleeding in hospitalized patients treated with anticoagulant therapy. Furthermore, the study was performed in two different types of hospitals, a University Medical Center and a general teaching hospital, which increases the generalizability of our findings. Another strength is the prospective design of the study. Finally, all bleeding events were evaluated and classified by two independent expert physicians in the field using internationally accepted ISTH criteria.

A few limitations of our study should be mentioned. First, data on bleeding were derived from reports of the responsible physicians noted in the electronic medical records (EMRs). This makes the study dependent on the information recorded by the responsible physician, which may lead to underreporting of the number of bleeding events. Second, the number of patients using concomitant interacting drugs was relatively low, decreasing the power to find significant associations between the use of concomitant interacting drugs and the risk of bleeding. Third, commonly used risk scores for bleeding such as the HAS-BLED score could not be used, as our patients are dissimilar to the study population this score was based on. Finally, this study was performed in patients using anticoagulants, without using a control group of patients who had a bleeding during hospitalization and did not use this type of drugs.

In conclusion, the prevalence of bleeding in anticoagulant users during hospitalization was 65 out of 906 patients (7.2%). This study detected potential risk factors that could help to identify patients on anticoagulants who have an increased risk of bleeding

during hospitalization. These findings can be used to identify patients at the highest risk of bleeding. Doing so allows for targeted interventions for the multidisciplinary antithrombotic team to reduce bleeding risk during hospitalization.

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Supplementary Table 1. Data collection

Part	Data content
Patient data	Patient ID
	Date of birth
	Gender
	Date of hospitalization
	Date of hospital discharge
	Deceased (yes/no)
	If deceased, date of death
	Type of hospital (University Medical Center/general teaching hospital)
	Bleeding in history (yes/no)
	Thrombocytopenia
	Cancer
Interventions	Surgical procedure (yes/no)
	If surgical procedure, bleeding risk of the surgical procedure (high, low, or clinically non-relevant)
	Non-surgical interventions (yes/no)
Medication data	Type of anticoagulant therapy
	• VKA monotherapy • DOAC monotherapy • LMWH monotherapy • VKA + LMWH • Combination of SAPT with a VKA or DOAC or LMWH • Combination of DAPT with a VKA or DOAC or LMWH
	Concomitant medication that increase the effect of VKAs:
	• Miconazole, cotrimoxazole, fluconazole, voriconazole and amiodarone
	Concomitant medication that increase the effect of DOACs:
	• Ketoconazole, itraconazole, voriconazole, cyclosporine, tacrolimus and verapamil
Clinical chemistry data	Laboratory values
	• e-GFR (ml/min/1.73m^2) on the day of hospitalization
Study outcome	Bleeding during hospitalization (yes/no)

e-GFR, estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) formula [16]; VKA, vitamin-K antagonist; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight-heparin; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy

Supplementary Table 2. Potential risk factors of major bleeding in hospitalized patients on anticoagulant therapies

Potential determinant	OR [95% CI]	ORadj [95% CI]
Female gender	**1.9 [1.1-3.4]**	**2.4 [1.3-4.5]**
Age, years	1.0 [1.0-1.0]	-
Bleeding in history	0.8 [0.4-1.6]	-
Cancer	1.2 [0.7-2.1]	
Hospital type		
General teaching hospital	Ref.	
University Medical Center	**2.1 [1.2-3.8]**	1.4 [0.7-2.7]
Surgery		
No surgery	Ref.	
High bleeding risk procedure	**7.0 [3.6-13.6]**	**7.6 [3.6-16.2]**
Low bleeding risk procedure	**5.3 [1.9-14.6]**	**5.6 [1.9-16.7]**
Clinically non-relevant bleeding risk procedure	1.2 [0.2-9.5]	1.0 [0.1-8.1]
Interventions		
No non-surgical interventions	Ref.	
Non-surgical interventions	**3.0 [1.4-6.2]**	**4.9 [2.0-11.6]**
e-GFR		
>50 ml/min/1.73m2	Ref.	
≤ 50 ml/min/1.73m2	1.0 [0.5-1.8]	-
Type of anticoagulant therapy		
VKA monotherapy	Ref.	
DOAC monotherapy	1.4 [0.3-6.6]	-
LMWH monotherapy	**3.3 [1.3-8.4]**	2.7 [1.0-7.3]
VKA + LMWH	**3.1 [1.3-7.5]**	1.9 [0.8-4.7]
Combination of SAPT with a VKA or DOAC or LMWH	**2.9 [1.2-7.5]**	2.1 [0.8-5.6]
Combination of DAPT with a VKA or DOAC or LMWH	0.9 [0.2-4.2]	-
Interacting drugs		
No VKA interacting drugs	Ref.	
VKA interacting drugs	1.8 [0.9-3.6]	-
Sensitivity analysis VKA interacting drugs		2.0 [0.9-4.4]

Numbers in bold are statistically significant. OR, odds ratio; 95%CI, 95% confidence interval; ORadj, adjusted odds ratio; e-GFR, estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) formula [16]; VKA, vitamin-K antagonist; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight-heparin; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy

Chapter 4

Anticoagulant medication errors in hospitals and primary care: a cross-sectional study

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ABSTRACT

Objective

To assess the proportion of all medication error reports in hospitals and primary care that involved an anticoagulant. Secondary objectives were the anticoagulant involved, phase of the medication process in which the error occurred, causes and consequences of 1000 anticoagulant medication errors. Additional secondary objectives were the total number of anticoagulant medication error reports per month, divided by the total number of medication error reports per month and the proportion of causes of 1000 anticoagulant medication errors (comparing the pre and post guideline phase).

Design

A cross-sectional study.

Setting

Medication errors reported to the Central Medication incidents Registration reporting system.

Participants

Between December 2012 and May 2015, 42 962 medication errors were reported to the CMR. Intervention: N/A.

Main outcome measure

Proportion of all medication error reports that involved an anticoagulant. Phase of the medication process in which the error occurred, causes and consequences of 1000 anticoagulant medication errors. The total number of anticoagulant medication error reports per month, divided by the total number of medication error reports per month (comparing the pre and post-guideline phase) and the total number of causes of 1000 anticoagulant medication errors before and after introduction of the LSKA 2.0 guideline.

Results

Anticoagulants were involved in 8.3% of the medication error reports. A random selection of 1000 anticoagulant medication error reports revealed that low-molecular weight heparins were most often involved in the error reports (56.2%). Most reports concerned the prescribing phase of the medication process (37.1%) and human factors were the leading cause of medication errors mentioned in the reports (53.4%).

Publication of the national guideline on integrated antithrombotic care had no effect on the proportion of anticoagulant medication error reports. Human factors were the leading cause of medication errors before and after publication of the guideline.

Conclusions

Anticoagulant medication errors occurred in 8.3% of all medication errors. Most error reports concerned the prescribing phase of the medication process. Leading cause was human factors. The publication of the guideline had no effect on the proportion of anticoagulant medication errors.

INTRODUCTION

Medication errors are one of the most common types of medical errors and cause significant morbidity and mortality [1-4]. A medication error is defined as any preventable event that may cause or lead to inappropriate medication usage or patient harm while the medication is in the control of the health care professional, patient or consumer [5]. The 1999 Institute of Medicine report, *To Err is Human*, stated that 44,000 to 98,000 hospitalized patients in the United States die each year because of medical errors [6]. In the Netherlands, the HARM (Hospital Admissions Related to Medication) study showed that 5.6% of all unplanned hospitalizations were drug-related and that 6.3% of these drug-related hospitalizations were attributable to anticoagulants [7].

A few studies characterized anticoagulant medication errors. Desai et al. described the characteristics, causes and outcomes of reported anticoagulant medication errors in nursing homes. They found that the documentation and monitoring phases of medication use were disproportionately involved in anticoagulation errors compared with other types of errors [8]. Fanikos and colleagues outlined characteristics and causes of reported anticoagulant medication errors in a hospital setting. Dosing errors accounted for nearly 68% of the 130 anticoagulant medication errors [9].

Given the fact that anticoagulants carry high risk for patient safety and are among the most frequently prescribed drugs involved in harmful medication errors [9-12] a multidisciplinary guideline was drafted in the Netherlands to provide a standard for antithrombotic therapy to provide optimal care to patients on antithrombotic therapy: the 'Landelijke Standaard Ketenzorg Antistolling' (LSKA; Dutch guideline on integrated antithrombotic care) [13].

Despite anticoagulants frequently being involved in medication errors, little is known about the characteristics of anticoagulation-related medication errors reported in hospitals and primary care.

Moreover, most studies focused on medication errors associated with warfarin or low-molecular-weight-heparin (LMWH) and do not concern patients using other vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) [8, 9].

Finally, the consequences of implementation of a guideline on the proportion of medication errors has not been investigated yet. The hypothesis is that interventions, such as introducing a new guideline lead to a short-term increase in medication error reports, but will lead to fewer medication error reports in the long-term. The immediate

increase in error reports may be due to the rising attention and higher awareness after publication of the guideline. This effect was also shown in an intervention study in the US. Weant et al. described an increase in the number of medication errors reported during the initial transition period after implementation of computerized prescriber order entry [14].

The primary aim of our study was to determine the proportion of medication error reports in hospitals and primary care in which anticoagulants are involved. Secondary goals were to describe the involved anticoagulant, phase of the medication process in which the error occurred, causes, and consequences within a subsample of 1,000 anticoagulant medication errors, and to analyze the influence of the publication of the national guideline on integrated antithrombotic care on the proportion and causes of reported anticoagulant medication errors.

METHODS

Design and setting

This study is designed as a retrospective cross-sectional study. The CMR (Central Medication incidents Registration) is a Dutch nationwide online registration system for medication error reports. The system is based on anonymous self-reports of medication errors by caregivers. Medication errors derived from internal reporting systems in hospitals and community pharmacies in the Netherlands are reported through a web-based CMR reporting form. The reporting form consists of three sections: administrative information, patient data, and information about the medication error. The description of the medication error starts with an open question to describe the medication error. The remaining questions are multiple choice questions with predefined answers in drop-down menus. The CMR screens, analyses and evaluates the reported medication errors. The support staff at the CMR organization consists of a clinical pharmacologist, a physician, a pharmacy technician, and a nurse [15]. The data for our study were collected from the CMR reports in an aggregated way. Access to the original error reports was not possible due to privacy constraints. Anticoagulant medication errors of the drugs listed in Table 1 reported to the CMR reporting system between December 2012 and May 2015 were collected. Haemostatic agents play a crucial role in anticoagulation therapy by reversing the anticoagulant effect when bleeding occurs. Therefore, we also included medication errors involving haemostatic agents.

Table 1. Included drugs

Group of anticoagulants (ATC code)	**Anticoagulants (ATC code)**
Vitamin K antagonist (B01AA)	Acenocoumarol (B01AA07)
	Phenprocoumon (B01AA04)
Low-molecular-weight-heparin (B01AB)	Dalteparin (B01AB04)
	Enoxaparin (B01AB05)
	Nadoparin (B01AB06)
	Tinzaparin (B01AB10)
Heparin (B01AB)	Heparin (B01AB01)
Direct thrombin inhibitor (B01AE)	Bivalirudin (B01AE06)
	Dabigatran etexilate (B01AE07)
Direct factor Xa inhibitor (B01AF)	Rivaroxaban (B01AF01)
	Apixaban (B01AF02)
Other anticoagulants (B01AX)	Fondaparinux (B01AX05)
Group of haemostatic agents (ATC code)	**Haemostatic agents (ATC code)**
Antihemorrhagics (B02)	Tranexamic acid (B02AA02)
	Phytomenadione (B02BA01)
	Human fibrinogen (B02BB01)
	Coagulation factor IX, II, VII and X in combination (B02BD01)
	Eptacog alfa (B02BD08)
	Protamin (V03AB14)

ATC, anatomical therapeutic chemical.

To determine the proportion of medication error reports that involved an anticoagulant; all CMR reports from December 2012 to May 2015 were included as denominator. The numerator consisted of the reports that involved an anticoagulant or haemostatic agent. The anticoagulant medication error reports were stratified on the origin of the report (hospital or primary care). Medication errors in primary care are mainly from community pharmacies since they have been reporting since March 2010, while general practitioners have been participating since 2015.

A random number generator in SPSS was used to select 1,000 anticoagulant medication errors, for detailed analysis. With 1,000 anticoagulant medication errors, we expect to have a representative sample of the total number of anticoagulant medication errors between December 2012 and May 2015. Within this subsample we analyzed the involved anticoagulant, phase of the medication process in which the error occurred, causes, and consequences of anticoagulant medication errors.

An antithrombotic 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). The first version of the LSKA guideline was published in 2012 focusing on the collaboration between health care providers at the local level of patients using VKAs. In July 2014, the second version of the LSKA guideline appeared. In addition to the collaboration at the local level, the LSKA 2.0 guideline focuses on the individual caregiver and the organization in the hospital and primary care. The LSKA 2.0 describes the tasks and responsibilities and how the communication and coordination takes place between health care providers at a regional level (thrombotic service, general practitioner, community pharmacist and hospital care) and the patient. Furthermore, the DOACs and platelet aggregation inhibitors were integrated in LSKA 2.0 guideline. As the LSKA 2.0 guideline covers the entire process of anticoagulant use, this may have caused an increase in anticoagulant medication error reports due to the raised awareness. This hypothesis was tested in the secondary objectives of this study.

Data collection

The following data of each error report, filled in by caregivers, were collected: date of error, origin of report (hospital or primary care), phase of the medication process in which the error occurred, cause of error, and consequences.

The phase of the medication process in which the error occurred, was divided into five categories: prescribing, transcribing and verifying, dispensing, administering and monitoring [16]. The medication surveillance type of error was incorporated into the prescribing category and the order entry of the prescription into the prescribing and transcribing/verifying categories. The classification of causes of error was based on the Eindhoven classification method, which discriminates between technical, organizational, communication, and human factors [17, 18]. The Dutch coding system for patient safety was used to classify the consequences of the error, divided into five classes: no harm, minimal/mild harm, serious temporary harm, serious permanent harm, and death [19].

For analysis of the effect of the LSKA 2.0 guideline on the proportion of medication errors, the total number of medication errors per month and the number of anticoagulant medication errors per month reported to the CMR were collected, both in the period before introduction of the LSKA 2.0 guideline (December 2012 until July 2014) and in the period after the guideline introduction (July 2014 to May 2015). To assess the effect of the LSKA 2.0 guideline on the proportion of causes of medication errors, the total

number of causes of 1,000 anticoagulant medication errors reported to the CMR were collected, both in the period before introduction of the LSKA 2.0 guideline and in the period after introduction of te LSKA 2.0 guideline.

Outcomes

Primary outcome was the proportion of all medication error reports in hospitals and primary care that involved an anticoagulant. Secondary outcomes were the anticoagulant involved, phase of the medication process in which the error occurred, causes and consequences of 1,000 anticoagulant medication errors. Additional secondary outcomes were the total number of anticoagulant medication error reports per month, divided by the total number of medication error reports per month (comparing the pre- and post-guideline phase) and the total number of causes of 1,000 anticoagulant medication errors before and after introduction of the LSKA 2.0 guideline

Data analysis

All data were processed with MS Excel 2010 and analyzed with SPSS version 21.0. Descriptive statistics were used to determine the proportion of anticoagulant medication reports and the involved anticoagulant phase of the medication process in which the error occurred, causes, consequences of 1,000 anticoagulant medication errors, and the influence of the publication of the LSKA 2.0 guideline on the proportion of causes of 1,000 anticoagulant medication errors.

For analysis of the influence of the publication of the LSKA 2.0 guideline on the proportion of anticoagulant medication errors we used segmented regression analysis for the interrupted time series (ITS) data. The anticoagulant medication errors were analyzed using months as data points (i.e., 19 data points before and 10 data points after the intervention of the time series). The interruption was the introduction of the guideline (July 2014). Durbin-Watson statistics was used to check for possible autocorrelation [20]. To estimate the level and trend of the percentage of anticoagulant errors before the publication of the antithrombotic guideline, and to estimate the changes in level and trend after the publication of the antithrombotic guideline, the following linear regression model was used: [21]

$Y_t = ß_0 + ß_1 * time_t + ß_2 * intervention_t + ß_3 * time\ after\ intervention_t + \mathbf{e}_t$
Y_0 = mean percentage at time is 0 = $ß_0$
$ß_1$ = baseline trend
$ß_2$ = immediate change after intervention
$ß_3$ = change in trend

RESULTS

From December 2012 to May 2015, 42,962 medication errors were reported to the CMR. Of these errors, 37,325 (87%) originated from hospitals and 5,637 (13%) from primary care. Anticoagulant medication errors were seen in 3,557 reports out of 42,962 (8.3%), of which 96% were reported by hospitals.

A random selection of 1,000 anticoagulant medication error reports was analyzed in more detail. 933 out of 1,000 (93.3%) anticoagulant medication errors were from the hospital. The most frequently reported medication classes were LMWHs (56.2%) and VKAs (27.7%). Heparins accounted for 6.8%, followed by haemostatic agents (4.3%). DOACs were the least frequently type of anticoagulant involved in the reports (3%).

Most anticoagulant medication errors were reported as prescribing errors (37.1%), followed by administering errors (29.8%). Detailed analysis identified incomplete prescription (16.1%) and ordered drug not given (11.1%) as the most commonly reported errors in these categories (Table 2).

Table 3 shows the causes of anticoagulant medication errors. Human factors are the most common causes mentioned in the medication error reports (53.4%). In this category, human performance deficit (failure to do what is known to be right), not following protocols and guidelines, and not performing the double-checking procedures are the most common reported errors.

In 982 (98.2%) medication error reports the consequences for the patient of the error were not reported. Twelve errors were reported to be associated with patient harm. Two of these errors resulted in death; one in serious permanent harm, six in serious temporary harm, three in minimal/mild harm and six in no harm.

Figure 1 shows the percentage of anticoagulant errors reported to the CMR during the study period. Anticoagulant medication errors were seen in 2,538 reports out of a total of 26,891 (9.4%) reports before introduction of the LSKA 2.0 guideline (December 2012 until July 2014) and in 1,019 reports out of 16,071 (6.3%) reports after the guideline introduction (July 2014 to May 2015).

Table 2. Phases of the medication process in which the anticoagulant medication error occurred

Phase of medication process	Reported errors of the phase of the medication process (n=1000) N (%)
Prescribing	**371 (37.1)**
Incomplete prescription	161 (16.1)
Wrong dose	33 (3.3)
Drug omitted from prescription	28 (2.8)
Wrong duration	24 (2.4)
Wrong time	18 (1.8)
Other	106 (10.6)
Transcribing and verifying	**216 (21.6)**
No prescription	37 (3.7)
No or incomplete medical information of the patient	34 (3.4)
Prescription has not been processed	28 (2.8)
Wrong duration	13 (1.3)
Wrong dose or frequency	13 (1.3)
Other	90 (9.0)
Dispensing	**81 (8.1)**
Ordered drug not dispensed	25 (2.5)
Wrong dose or frequency	12 (1.2)
Wrong strength	11 (1.1)
Wrong drug	10 (1.0)
Expired product	4 (0.4)
Other	19 (1.9)
Administering	**298 (29.8)**
Ordered drug not given	111 (11.1)
Given drug not ordered	40 (4.0)
Wrong dose or frequency	34 (3.4)
Wrong time	33 (3.3)
Wrong duration	11 (1.1)
Other	68 (6.8)
Monitoring	**32 (3.2)**
Insufficient monitoring	18 (1.8)
Incorrect actions based on monitoring results	12 (1.2)
Other	1 (0.1)
Unknown	**2 (0.2)**

Table 3. Causes of anticoagulant medication errors

Cause of medication error	**Reported cause of errors (n=1300) N (%)**
Technical	**70 (5.4)**
Errors in the electronic prescribing system	44 (3.4)
Medication name confusion	15 (1.2)
Other	11 (0.8)
Organizational	**111 (8.5)**
Unclear protocols or guidelines	30 (2.3)
High work pressure and short-staffed	21 (1.6)
No protocol or guidelines	12 (0.9)
Protocol or guideline not implemented	12 (0.9)
Other	24 (1.8)
Communication	**124 (9.5)**
Unclear communication between caregivers	33 (3.2)
Wrong transfer of information between caregivers	33 (3.2)
No transfer of information between caregivers	28 (2.2)
Wrong communication to the patient	21 (1.6)
Other	9 (0.7)
Human factors	**694 (53.4)**
Performance deficit*	305 (23.5)
Protocols or guidelines not followed	162 (12.5)
No double-checking performed	159 (12.2)
Insufficient expertise	63 (4.8)
Other	5 (0.4)
Unknown	**301 (23.2)**

*Failure to do what is known to be right

	Y_0 (95% CI) (mean percentage at time=0)	$ß_1$ (95% CI) (baseline trend)	$ß_2$ (95% CI) (immediate change)	$ß_3$ (95% CI) (change in trend)
Anticoagulant errors	**12.78*** **(8.79; 16.77)**	-0.19 (-0.54; 0.16)	2.57 (-3.97; 9.10)	-0.64 (-1.51; 0.23)

*Significant values are in bold type face

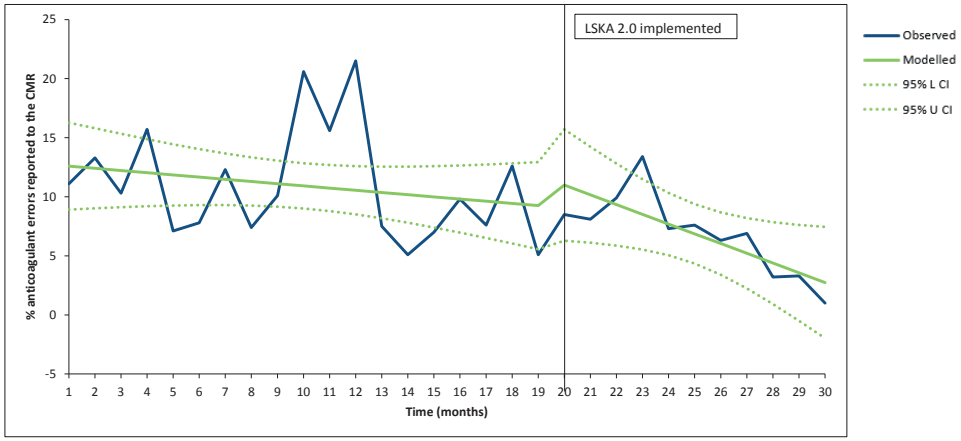

Figure 1. Impact of Landelijke Standaard Ketenzorg Antistolling, version 2 (LSKA; Dutch guideline on integrated antithrombotic care) on percentage of anticoagulant errors reported to the CMR

The publication of the LSKA 2.0 guideline was associated with an immediate increase in level of 2.57% (95% CI: -3.97, 9.10%) of anticoagulant errors ($ß_2$), and a change in trend of -0.64% (95% CI: -1.51, 0.23) per month ($ß_3$). A trend of -0.19% (95% CI: -0.54, 0.16%) of anticoagulant errors was observed at baseline. The change in level and change in trend were not statistically significant.

No significant autocorrelation was detected for any of the outcome parameters presented (Durbin–Watson value of 1.7).

Table 4 shows the proportion of causes of 1,000 anticoagulant medication errors before and after introduction of the LSKA 2.0 guideline. Both before (55.7%) and after (47.9%) publication of the LSKA 2.0 guideline, human factors were the leading cause of medication errors.

Table 4. Impact of Landelijke Standaard Ketenzorg Antistolling, version 2 (LSKA; Dutch guideline on integrated antithrombotice care) on percentage of causes of 1,000 anticoagulant errors reported to the CMR

Cause of medication error	Reported cause of errors before LSKA 2.0 guideline: December 2012 until July 2014 (n=918*) N (%)	Reported cause of errors after LSKA 2.0 guideline: July 2014 to May 2015 (n=382*) N (%)
Technical	51 (5.6)	19 (5.0)
Organizational	81 (8.8)	30 (7.9)
Communication	87 (9.5)	37 (9.7)
Human factors	511 (55.7)	183 (47.9)
Unknown	188 (20.5)	113 (29.6)

*A medication error may result from multiple causes

DISCUSSION

This study revealed that anticoagulants were found to be frequently involved in medication error reports, one of every twelve reported errors (8.3%). This is comparable to anticoagulant-related medication errors in previous studies [8, 9]. Fanikos et al. reported that 7.2% of all medication errors in the hospitalized patient were caused by anticoagulants and Rishi et al. found that in 1 in 20 medication errors in nursing homes an anticoagulant was involved. The hospital is more active in reporting of medication errors to the CMR than primary care. This is shown by the fact that 87% of the errors were reported by hospitals. The small number of reported errors from primary care (community pharmacies and general practitioners) is comparable with two studies where 8.5% and 6% of the errors came from primary care [22, 23]. A possible explanation for the larger number of reported errors by hospitals is the reporting culture. Contrary to primary care, in hospitals there are more staff members to report and there is a dedicated person for medication safety. Moreover, hospitals can report to the CMR reporting system since 2006, while community pharmacies participated since 2010 and general practitioners since 2015. Therefore hospitals have more experience with the reporting of errors to the CMR reporting system. In addition, because treatment with anticoagulants is often initiated in the hospital, the majority of anticoagulant medication errors will come from hospitals. Another possible reason for the small number of reported errors from primary care may be due to the influence of the thrombosis services. In the Netherlands, treatment with VKAs in primary care is mostly carried out by medical doctors in well-organized thrombosis services. These medical doctors are specialized in this task and have a lot experience with this patient population, which could result in less medication errors.

VKAs were the most commonly used anticoagulants in the Netherlands at the time of this study [24]. Nevertheless, the low-molecular-weight-heparins were most often associated with reported medication errors. LMWHs are frequently used for bridging during perioperative interruption of VKA treatment in the hospital. Bridging anticoagulation therapy is a complex procedure with a high risk of errors [25]. Henriksen et al. found that admission to or discharge from hospital, or undergoing surgery was associated with the highest number of serious and fatal adverse medication incidents. This was supported by medication incidents related to prescribing situations such as bridging. During surgery, prescribing excess anticoagulant was the most frequent problem.

In our study we found that DOACs were least often associated with reported anticoagulant medication errors. A possible explanation is the greater ease of use (no need for laboratory monitoring, and administering of fixed dose) [26], fewer drug and food interactions, and wider therapeutic window of DOACs compared with VKAs. The use of DOACs, however, was substantially less than the other anticoagulants, as only 10% of the patients in the Netherlands used DOACs at the time of our study [27]. This low use in itself can also be an explanation for the low number of errors related to DOACs.

This study showed that anticoagulant medication errors were most often reported during the prescribing phase and administering phase of the medication process. These results are in line with prior studies that found the majority of reported medication errors in the prescribing and administering phase [9, 28-32]. Fanikos et al. found that errors with anticoagulant therapy were most often seen during drug administration, whereas Winterstein et al. and Samsiah et al. reported the most medication errors during the prescribing phase [9, 28, 32].

In our study, human factors were most often mentioned as cause of the reported anticoagulant medication errors (53.4%). The most frequent types of human factors were: human performance deficit (23.5%), not following protocols and guidelines (12.5%) and not performing double-checking of medication (12.2%). This corresponds with previous results of Zhan et al. who showed that human performance deficit and not following procedures and protocols were among the most common causes of warfarin errors in hospitals and outpatient facilities [33]. The same causes of errors were seen in the study of Pham et al., who reported that 29% of the medication errors in emergency departments were caused by human performance deficit and 17% by not following procedures and protocols [29].

Our study showed no statistical significant effect on the proportion of reported anticoagulant medication errors after publication of the national guideline on integrated antithrombotic care. Circumstances other than the implementation of a guideline (i.e. introduction of the DOACs) could have affected the number of reported anticoagulant medication errors. Another reason for not finding a significant effect may be that the publication of the second version of the LSKA guideline had less impact than the first version of the LSKA guideline published in 2012. The lack of effect may be explained by the limited number of monthly data points after publication of the guideline of the time series. Because implementation of a guideline takes time and does not improve care itself, active methods, such as education are needed to improve the awareness of the guideline. A change in trend after publication of the LSKA 2.0 guideline may be suggested in Figure 1, although it did not reach statistical significance.

This study showed that human factors were the leading cause of anticoagulant medication errors before and after publication of the LSKA 2.0 guideline.

Our study has several limitations. First, reporting of medication errors to the CMR reporting system is voluntary. Underreporting, selective reporting and incomplete reporting of medication errors are widely seen in voluntarily self-reporting systems [34]. A second limitation is that we did not analyze the total number of anticoagulant medication errors reported to the CMR in detail, but a random selection of 1,000 errors to describe the anticoagulant involved, phase of the medication process in which the error occurred, causes, and consequences. Third, in 982 (98.2%) medication error reports the consequences for the patient were unknown. Due to the large number of missing values for anticoagulant medication errors leading to harm, definite conclusions can not be drawn.

Finally, because implementation of a guideline takes time, it is possible that the influence of the LSKA 2.0 guideline on the frequency of anticoagulant medication errors in our study is limited and its influence after implementation may become apparent only after some time. Despite these limitations, our study is the first study describing the influence of a national guideline on integrated antithrombotic care on the proportion of anticoagulant medication errors using an interrupted time series approach.

To conclude, anticoagulant medication errors are frequently reported. Low-molecular-weight-heparins were most often reported as causative agent. Especially the prescribing and administering phases were involved in anticoagulant errors. The majority of errors made in the prescribing phase arose from incomplete prescriptions. Omission errors (ordered drug not given) were responsible for the highest percentage of errors in the

administering phase. Human factors, such as performance deficit and not following protocols and guidelines were the most common causes of reported anticoagulant medication errors, before and after the introduction of the LSKA 2.0 guideline. Interventions should focus on these causes, for example by introducing computerized physician order entry in which incomplete prescriptions are impossible. Future research is needed to determine the impact of such interventions on the number of anticoagulant medication errors. These future studies should also take into account the presence of bias in voluntarily self-reporting systems.

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Part 2/2

Antithrombotic stewardship

Chapter 5

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 of medication 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 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 hospitalization.

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 that 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 endpoint consisting of ≥1 bleeding or ≥1 thrombotic event from the beginning of antithrombotic therapy (or hospitalization) until 3 months after hospitalization. Bleeding is defined according to the 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 Erasmus University Medical Center. The findings of the study will be disseminated through peer-reviewed journals and presented at relevant conferences.

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 hospitalizations in The Netherlands were drug-related and that 46% of these were potentially preventable. Anticoagulants belong to the top 5 of medication 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 optimization of therapy [6]. Analogous to the A-teams, multidisciplinary antithrombotic teams (in Dutch 'Stollingsteam' or S-team) focusing on anticoagulants can be made responsible for LSKA implementation, can provide expertise to support the care of both in- and out-patients alike, ensure adequate transitioning of patients from the in- to the out-patient 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 centers indicated that their antithrombotic service was multidisciplinary [7]. Padron et al. describe an expanded antithrombotic stewardship, including both DOAC treatment and facilitating care after hospital discharge [8]. It concerned a US single center pharmacist-directed stewardship. Only a small retrospective control group (n=12) was included in the study. A total of 409 patients on anticoagulation 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 et al. 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 regards 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 hospitalization, 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 hospitalization.

METHODS AND ANALYSIS

Study design

A prospective non-randomized 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 (pre-implementation measurement) and an intervention group (post-implementation measurement) will be compared. First, patients are included during nine months in the usual care group (pre-implementation phase with three months follow-up). Second, the intervention is implemented (implementation phase of 3 months). Finally, patients are included during nine months in the intervention group (post-implementation phase with three months follow-up, see figure 1 for flowchart).

Figure 1. Phases during the study

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 center 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 that 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 table 1 or 2. Exclusion criteria are the following: 1) no informed consent from the patient (or the parents/guardian of the patient), 2) patients with hospital stays of less than 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 anticoagulation therapy, 6) patients treated with phytomenadione for the prevention and treatment of vitamin K deficiency, 7) patients treated during hospitalization with a single dose of an anticoagulant medicine. Only the patient's first hospital admission is included in the study period (readmission is an endpoint).

Study procedures

Usual Care

During the pre-implementation 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 contra-indications.

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

Table 1. Antithrombotics*

Group of anticoagulants (ATC code)	Anticoagulants (ATC code)
Vitamin K antagonists (B01AA)	Phenprocoumon (B01AA04)
	Acenoucoumarol (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.

Table 2. Hemostatic agents*

Group of hemostatic agents (ATC code)	Hemostatic 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 hemostatic 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.

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 in- and outside the hospital In the current situation, hospital residents and/or hematologists 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 hematologists.

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 specialized thrombosis nurse as case manager, hematologist, a pediatric hematologist, medical leader regional Thrombotic Service (responsible for outpatient management of VKA treatment), hospital pharmacist/clinical pharmacologist, cardiologist, anesthesiologist, pulmonologist, neurologist, surgeon and quality officer. In the Reinier de Graaf Hospital the team will consist of a specialized thrombosis nurse as case manager, hematologist, medical leader regional Thrombotic Service, hospital pharmacist/clinical pharmacologist, cardiologist, anesthesiologist and a neurologist. A pulmonologist, dermatologist, clinical chemist, pediatrician, emergency physician and (orthopedic) 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 optimizing treatment with anticoagulants. The pharmacotherapy review focuses on dosing (e.g. in relation to decreased renal function), double medication, drug-drug interactions, contra-indications 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 anticoagulation therapy and how to safely care for it on a daily basis.

Medication reconciliation at discharge At discharge medication reconciliation is performed by the specialized thrombosis nurse and the hospital pharmacy. Discrepancies with the pre-admission 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 in- and outside the hospital To further support the cooperation between primary care (Thrombotic Service, the general practitioner, and the community pharmacist) and the hospital care, consultation is offered from the professionals in the multidisciplinary antithrombotic teams.

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

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

Data collection

Outcome measures

The primary outcome of this study is the proportion of patients with a composite endpoint consisting of ≥1 bleeding (major bleeding and non-major bleeding) or ≥1 thrombotic event from the beginning of antithrombotic therapy (or hospitalization) until 3 months after hospitalization. Bleeding is defined according to the 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 hospitalization. For collection of the post-discharge outcomes, validated questionnaires are used. Three months after hospitalization 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 pre-implementation and post-implementation period.

Table 3. Data collection; content of case report form (CRF)

Part	Data content
Patient data	Patient ID
	Date of birth*
	Gender*
	Weight on the first day of hospitalization*
	Community pharmacist*[$]
	Reason for hospitalization*
	Reason for exclusion
	(Co)morbidity*
	Day of hospitalization*
	Hospital discharge date*
	Any surgery (coded with Verrichtingen code[12]) or diagnosis during hospitalization*
Study outcomes	Bleeding (major bleeding and non-major bleeding) event(s) during hospitalization*
	Bleeding (major bleeding and non-major bleeding) event(s) within 3 months after hospitalization[^]
	Severity of bleeding complication
	Location of bleeding complication
	Thrombotic event(s) during hospitalization*
	Thrombotic event(s) within 3 months after hospitalization[^]
	Severity of thrombotic complication*
	Location of thrombotic complication
	Date of each readmission in the following 3 months after the first hospitalization*[^]
	The reason for readmission[^]
	Quality of life (3 months after discharge):[$] • Age 0-3: no EQ-5D-Y available • Age 4-7: EQ-5D-Yproxy version 1 • Age 8-11: EQ-5D-Y or EQ-5D-Y proxy version 1 • Age 12-15: EQ-5D-Y or EQ5D • Age 16 and older: EQ5D
	Adherence by the patient to the therapy; MARS5 (3 months after discharge)[$]
	Patient satisfaction of the anticoagulation therapy; VAS satisfaction scale (3 months after discharge)[$]
	Adherence to the hospital protocol
	Percentage of time in therapeutic range (TTR) of vitamin K antagonists during hospitalization and as an outpatient during 3 months follow-up*
	All-cause mortality*[+]
	Healthcare costs*

Table 3. Continued

Part	Data content
Clinical chemistry data	Laboratory values and the date of determination*+ • International Normalized Ratio (INR) • Activated Partial Thromboplastin Time (APTT) • Prothrombin time (PT) • Diluted Thrombin Time (dTT) • Hemoglobin (Hb) • Antifactor Xa (Anti-Xa) • Creatinine • Hematocrit (HT) • Erythrocytes • Thrombocytes • Estimated Glomerular Filtration Rate (eGFR) • Weight (Available clinical chemistry data are collected from 3 months before inclusion until 3 months after hospitalization)
Medication data	Medication use during hospitalization (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 three months before hospitalization (coded with ATC-code[13])+
	Overview of medication use three months after hospitalization (coded with ATC-code[13])+

* Obtained from the medical record of the hospital information system
+ Obtained from the community pharmacist and the Thrombosis Service
$ 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 hospitalization

The following parameters are registered:

- Major bleeding and non-major bleeding events during and 3 months after hospitalization: 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 hemodynamic instability) [16]. The ISTH definitions (table 4) are used to determine the severity of the bleeding event.

Table 4. International Society of Thrombosis and Haemostasis (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 hemoglobin 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 hemoglobin 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 h to the bleeding, and/or 4. Surgical site bleeding that requires a second intervention (open arthroscopic, endovascular) or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection, and/or 5. Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin 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 h to the bleeding.
Non-major bleeding	All bleeding events that do not meet the ISTH criteria according to which major bleeding is defined.

- Thrombotic events during and 3 months after hospitalization: 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

hospitalization, medication use during hospitalization, laboratory values, (co) morbidities classified according to Garcıa-Olmos et al. [21] and any surgery or diagnosis during hospitalization.

- Readmissions within 3 months after discharge.
- The quality of life is measured by the EuroQol EQ5D (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 (MARS; Medication Adherence Rating Scale) [25-28].
- The patient satisfaction of the anticoagulation therapy is measured by the VAS 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 (e.g. in relation to decreased renal function, age, body weight), perioperative bridging of anticoagulants, double medication and contra-indications.
- All-cause mortality: the hospital information system is used to register the date of death and the cause of death. The patient's general practitioner is asked for the date of death and the cause of death 3 months after hospitalization.
- Percentage of time in therapeutic range (TTR) of patients on vitamin K treatment during hospitalization and as an outpatient during 3 months follow-up: the INR data during hospitalization from the electronic medical record are collected by a specialized department in both hospitals. The INR data 3 months after hospitalization are obtained from the Thrombosis Service. Time in therapeutic INR range (TTR) is a way of summarizing INR control over time. A TTR of 70-80% is desirable [30], and according to European guidelines, TTR should be above 70% [31]. Time in therapeutic range was calculated according to F.R. Roosendaal's algorithm with linear interpolation [32].
- Medication use three months before and three months after hospitalization: medication records of the community pharmacy can be consulted through a link in the hospital information system for patients that 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.

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 cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: • Symptoms of ischemia • New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (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 computed tomography, transesophageal echocardiography, pulmonary arteriography, or computed tomography angiography.
Any objectively determined arterial or venous thrombus	Non-cerebral, non-cardiac arterial thrombotic or embolic events.

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 anticoagulants (or hospitalization) until 3 months after hospitalization. Economic analysis will be performed from a health care system perspective taking all health care 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 (e.g. hospitalization, medication, bleeding and thrombotic events) and out-patient health care costs (e.g. general practitioner) will be assessed.

Actual medical costs will be calculated by multiplying volume of health care use with corresponding unit prices.

For the intervention the full costprice will be calculated following the micro-costing 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, the training program, will be calculated for the S-team intervention. For the other health care 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 endpoint consisting of ≥1 bleeding (major bleeding and non-major bleeding) or ≥1 thrombotic event during and 3 months after hospitalization between the intervention and usual care.

Data monitoring

Data are collected on questionnaires (hard copy) and on a case report form (CRF) using Open Clinica®. Open Clinica is an open source clinical trial software for Electronic Data Capture (EDC) Clinical Data Management (CDM). Data entry errors are minimized by using multiple choice options and fixed data fields. In the Open Clinica 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 the study is complete, accurate, and verifiable. Open Clinica validates the file format and performs validity checking for the data. Access to Open Clinica is secured by a password.

Sample size calculation

Annual bleeding rates are 2-3% depending on the type of anticoagulant [35, 36], but in every day practice it seems 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 this is the rate we could achieve with the S-team and that the rate is 4% in the pre-implementation 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 pre-implementation phase and 917 patients in the post-implementation 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. But because our study is in hospitalized patients (and shortly after hospitalization), we assume that this present a period of instability for the patient, leading to relatively high event rates.

Based on 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. Due to the limited availability of study personnel, it is possible to recruit 3 patients per day per hospital. A random number generator will be used to select these 3 patients. With this inclusion rate, we expect to have included the necessary number of patients in a 9 months pre-implementation period and in a 9 months post-implementation period.

Data analysis

For the primary endpoint (the proportion of patients with a composite endpoint consisting of ≥1 bleeding (major bleeding and non-major bleeding) or ≥1 thrombotic event from the beginning of antithrombotic therapy (or hospitalization) until 3 months after hospitalization) 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 post-implementation data. The study design thus meets the criteria for a robust interrupted time series analysis, that is 3 periods of data-points pre- and post-implementation, each consisting of at least 30 patients [38, 39, 40]. The primary outcome will be compared using univariate and multivariate logistic regression. Sub-analyses will be performed for each type of anticoagulant and for hospital type in relation to bleeding and thrombotic events. In addition, in-hospital and post-discharge events will be analyzed 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 anticoagulation therapy, adherence to the hospital protocol, healthcare costs, all-cause mortality and the percentage of time in therapeutic range of vitamin K antagonists). To assess whether differences between pre-implementation and post-implementation periods may be explained by other factors, i.e. 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 chi-square test).

ETHICS AND DISSEMINATION

Ethical approval

This study protocol was approved by the Medical Ethical Committee of the Erasmus university medical center on 30 June 2015 (registration number: 2015/386). 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 endpoint 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. Because of this we were able to optimize 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 center and a general teaching hospital. This will enhance the generalizability. Third, a substantial number of patients is to be included. We anticipate having little problems in recruiting patients in order to ensure sufficient statistical power which should enable 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 not only inside the hospital but also outside the hospital.

This study also has some limitations. First, using questionnaires for collection of several secondary outcomes may suffer from response bias. This will be minimized as much as possible by contacting the patients by telephone when the questionnaires are not returned within two weeks. Second, despite the fact that it is a multicenter 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 hospitalization 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 non-randomized before-and-after study, without a retrospective control group. Improvements may already have been implemented during the pre-implementation 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 endpoint consisting of bleeding and thrombotic events. If such a team proves to be effective, implementation in hospitals will be recommended.

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Chapter 7

The effect of hospital-based antithrombotic stewardship on adherence to anticoagulant guidelines

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ABSTRACT

Background

Anticoagulant therapy is associated with a high risk of complications. Adherence to anticoagulant therapy protocols may lower this risk but adherence is often suboptimal. The introduction of a multidisciplinary antithrombotic team may improve adherence to anticoagulant guidelines among physicians.

Objective

To determine the effect of hospital-based multidisciplinary antithrombotic stewardship on adherence to anticoagulant guidelines among prescribing physicians.

Setting

This prospective non-randomised before-and-after study was conducted in patients hospitalized between October 2015 and December 2017 and treated with anticoagulant therapy.

Method

A multidisciplinary antithrombotic team focusing on education, medication reviews, drafting of local anticoagulant therapy protocols, patient counseling and medication reconciliation at admission and discharge was implemented in two Dutch hospitals.

Main outcome measure

Primary outcome was the proportion of the admitted patients in which the prescribing physician did adhere to the anticoagulant guidelines.

Results

The study comprised 1,886 patients, of which 941 patients were included in the usual care period and 945 patients in the intervention period. Multivariable logistic regression analysis indicated that adherence was observed significantly more often during the intervention period (adjusted odds ratio [ORadj] 1.58, 95% confidence interval [95% CI] 1.21-2.05). Detailed analysis identified that the significantly higher overall adherence in the intervention period was attributed to dosing of LMWHs (odds ratio [OR] 1.58, 95% CI 1.16-2.14).

Conclusion

This study shows that introduction of a multidisciplinary antithrombotic stewardship leads to a significantly higher overall adherence to anticoagulant guidelines among prescribing physicians, mainly based on the improvement of dosing of low-molecular-weight-heparins.

INTRODUCTION

Anticoagulant therapy is associated with a high risk of complications [1-3]. Medication errors with anticoagulants are among the most common causes leading to harm [4, 5]. Guidelines and protocols are developed to improve prescribing quality and thus patient outcomes, and to reduce variation in clinical practice [6]. However, a discrepancy exists between recommended care and daily clinical practice [7]. In earlier studies of non-adherence to guidelines concerning proton pump inhibitor prescription in hospitalized patients who are prescribed NSAIDs, diabetes medication and dosing of medication in patients with impaired renal function, non-adherence by physicians varied between 33% and 70% [8-10].

Studies evaluating partial and/or complete compliance with the American College of Chest Physicians (ACCP) venous thromboembolism (VTE) prevention guidelines, published between 2005 and 2008, showed that compliance rates ranged from 2.8% to 84% [11]. Proietti and colleagues assessed adherence in a cohort of atrial fibrillation (AF) acutely admitted patients. They concluded that only 40.9% of the patients were treated according to the European Society of Cardiology (ESC) guideline and guideline-adherent treatment was independently associated with a significantly lower risk of all-cause and cardiovascular (CV) death [12].

Several strategies to improve guideline adherence have been described. Education programs together with computer-based clinical decision support systems showed significant improvements in adherence to guidelines for venous thromboembolism in hospitals [13]. Bos et al. showed that education of hospital prescribers combined with audit and feedback by hospital pharmacists reduced physician non-adherence to guidelines covering pain management, antithrombotics, fluid and electrolyte management, application of radiographic contrast agents and surgical antibiotic prophylaxis [14]. Furthermore, Maynard and colleagues evaluated the impact of the implementation of a multidisciplinary team on inpatient anticoagulation and management of venous thromboembolism in 189 patients with 211 identified VTE events [15]. Interventions consisted of education, computer prescriber-order-entry system (CPOE) upgrades, clinical decision support, triggered consultation, and checklists. Warfarin adjustment by protocol improved from 70% to 96% and warfarin-heparin overlap improved from 26% to 74% after the implementation of the multidisciplinary team. However, compliance to low-molecular-weight heparins (LMWHs) showed no increase and mortality and readmission rates did not change significantly. The results from previous studies showed that compliance with guidelines of different drugs varied widely and that compliance depends not only on type of drug but also on the clinical

situation in which the drug is prescribed (e.g. acute care versus ambulatory care) [8-10]. Of course, depending on the situation other factors such as patient preferences may be more important than strict adherence to the guideline. Nevertheless, literature clearly shows there is room for improvement. Despite the fact that the same compliance with the prescribing guidelines for all drugs cannot be expected, there is still room for improvement. Moreover, existing anticoagulant intervention studies focused on patients treated with warfarin or low-molecular-weight-heparins (LMWHs) and do not concern patients using other vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs).

Aim of the study

The primary aim of our study was to determine the effect of hospital-based multidisciplinary antithrombotic stewardship on adherence to anticoagulant guidelines by prescribing physicians.

Ethics approval

Approval was obtained from the Medical Ethics Committee of the Erasmus University Medical Center (MEC-2015-386).

METHODS

Study design

This study was designed as a prospective non-randomized before-and-after study, with the intervention being the implementation of a multidisciplinary antithrombotic team. Therefore a 9-month period of usual care and a 9-month intervention period were compared.

This study was a sub-study of a larger antithrombotic stewardship study (S-team study), in which the effect of a multidisciplinary antithrombotic team was evaluated on the safety and efficacy of antithrombotic therapy during hospitalization [16].

Study setting

The study was conducted in the Erasmus University Medical Center (EMC) and the Reinier de Graaf Hospital (RdGG). The EMC is a 1320-bed University Medical Center based in Rotterdam, the Netherlands. The RdGG is a general teaching hospital located in Delft, the Netherlands, with 590 beds.

Study population

Patients admitted to the EMC or RdGG between October 2015 and December 2017 and treated with anticoagulant therapy were eligible for inclusion. The study population consisted of patients who started on anticoagulant therapy in the hospital, patients who were already treated with anticoagulant therapy before hospitalization and patients who restarted anticoagulant therapy after a surgical or non-surgical intervention. Only the patient's first hospital admission was included. All participants provided informed consent during hospitalization. Exclusion criteria were the following: (1) no informed consent from the patient (or the parents/guardian of the patient), (2) hospitalization for less than 24 hours, (3) admission to the intensive care unit (ICU) without previous admission to a general care ward, (4) patients who received only LMWHs as thrombosis prophylaxis.

Data collection

Data were collected from electronic patient records in the hospital information systems (HiX; Chipsoft, Amsterdam, the Netherlands and Elpado; homegrown system Erasmus University Medical Center, Rotterdam, the Netherlands) (Table S1). The bleeding risk of the surgical procedure (high, low, and clinically non-relevant bleeding risk) was defined according to the 'Richtlijn Antithrombotisch Beleid' (Dutch guideline on antithrombotic policy) [17]. Patient data were coded according to Dutch privacy guidelines. Data were collected during hospital stay from the day of hospitalization or from the day of discharge from the ICU to a general care ward until discharge from hospital or patient death. In patients who were initially admitted to a general care ward and subsequently transferred to the ICU, data were collected from the day of hospitalization until admission to the ICU. All data were processed with Open Clinica (Open Clinica LLC, Waltham, USA).

Usual care

During the usual care period the normal procedures of medication surveillance by hospital pharmacists and physicians were maintained. 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 alerts with a pop-up in case of drug-drug interactions, over- or underdose (dose ranges dependent on age, bodyweight and gender), duplications and contraindications. These medication surveillance alerts were easily dismissible by physicians. Furthermore, clinical rules were used in patients using DOACs or LMWHs. Clinical rules combine the renal function of the patient with the prescribed drug

to assess whether dose adjustments should be made based on the renal function. A detailed description of the procedures during the usual care period can be found in the study protocol [16].

Intervention

The previously published study protocol provides a detailed description of the antithrombotic team [16]. The intervention consisted of the implementation of a multidisciplinary antithrombotic team. The team in the University Medical Center consisted of a specialized thrombosis nurse as case manager, a hematologist, a pediatric hematologist, a hematologist (head) of the regional thrombosis service, a hospital pharmacist/clinical pharmacologist, a cardiologist, an anesthesiologist, a pulmonologist, a neurologist, a (vascular)surgeon and a quality officer. In the general hospital, the team consisted of a specialized thrombosis nurse as case manager, a hematologist, a hospital pharmacist, a cardiologist, an anesthesiologist and a clinical chemist. A neurologist, pulmonologist, pediatrician, emergency physician and (orthopedic) surgeon were added to the team when necessary. The teams focused on the following interventions:

- *Education*: To increase the knowledge of antithrombotic therapy among physicians, nurses and hospital pharmacists, hospital-wide education was given.
- *Medication reviews by (hospital) pharmacists*: Daily structured medication reviews were performed by the (hospital) pharmacist focused on optimizing treatment with anticoagulants. The pharmacotherapy review focused on dosing (i.e., in relation to decreased renal function, body weight and age), duplicate medication, drug–drug interactions, contraindications and perioperative bridging of anticoagulants.
- *Antithrombotic therapy guidelines*: Local guidelines were drafted based on recent national guidelines and updated to ensure there was a uniform policy on antithrombotic therapy.
- *Patient counseling*: The purpose of patient counseling was to provide information and education to patients with the aim of giving the patient more control and responsibility over their own health and healthcare. Such patient empowerment was performed on daily basis for each included patient.
- *Medication reconciliation:* At admission, data from the patients thrombosis service regarding dosing scheme, indication for anticoagulation, type of VKA, INR measurements and the INR target range were handed over to the responsible physician. At discharge, pharmacotherapy advice from the medication review were handed over to either the thrombosis service or the general practitioner, and to the community pharmacist.

Guidelines

Adherence to anticoagulant guidelines was assessed by using prevailing anticoagulant therapy guidelines which are implemented in the local hospital protocols. Seven guidelines were selected at which the adherence was easy to score. The guidelines focused on drug-drug interactions in patients using VKAs, dosing of LMWHs in relation to renal function and bodyweight and perioperative bridging of anticoagulants. The four separate guidelines regarding direct oral anticoagulants (drug-drug interactions in patients using DOACs, dosing of rivaroxaban versus renal function, dosing of dabigatran versus renal function and age, and dosing of apixaban versus serum creatinine, body weight and age) were clustered for the analysis into one pharmacotherapeutic DOAC measure because of the low number of DOAC users, resulting in a total of four guidelines. Table 1 shows the prevailing anticoagulant guidelines.

Outcome measures

Primary outcome was the proportion of the admitted patients in which the prescribing physician adhered to one or more of the anticoagulant guidelines (the total number of admitted patients was included as denominator). Secondary outcome was the proportion of the prescriptions in which the prescribing physician adhered to each of the four anticoagulant guidelines (for the prescribed anticoagulant(s) each patient was on, the total number of applicable guidelines and opportunities for adherence was calculated and included in the denominator).

Sample size

This study has been powered on the outcome measure of the S-team study, in which the effect of a multidisciplinary antithrombotic team on the safety and efficacy regarding antithrombotic therapy during hospitalization is studied [16]. With a type 1 error of 0.05, power of 80%, the required sample size was 917 patients in the usual care period and 917 patients in the intervention period. In order to account for drop-outs, 1900 patients were included.

Data analysis

All data were analyzed with IBM SPSS version 21.0 (IBM Software, New York, USA). All continuous variables were tested for normality with the Shapiro-Wilk test. Non-normal variables were expressed as medians and interquartile ranges (IQR) and differences between groups tested with the Mann-Whitney *U* test. Categorical variables were presented as percentages and tested for statistical significance between groups using the Chi square test. $P < 0.05$ was considered to be statistically significant. Odds ratios (OR) and 95% confidence intervals (95% CI) for each of the four anticoagulant guidelines

Table 1. Guidelines based on prevailing anticoagulant therapy guidelines

Pharmacotherapeutic measure	Effectuation measurement of protocol adherence	Reference
1. VKA and interacting drugs *cotrimoxazole, miconazole, fluconazole, voriconazole, amiodarone, rifampicin, rifabutin and rifaximin*	All patients with an active prescription of interacting drugs at the same time the VKA was prescribed, were checked whether the VKA or the interacting drug was discontinued and replaced by an alternative drug 24 hours after the start of the combination OR whether the INR was monitored after starting the combination of the interacting drug and the VKA (within 36 hours after the start of the combination with cotrimoxazole, miconazole, fluconazole, voriconazole and amiodarone AND within 5 days after the start of the combination with rifampicin, rifabutin and rifaximin).	Dutch national G-standard [18] SmPC VKA [19]
2a. DOAC and interacting drugs *ketoconazole, itraconazole, voriconazole, cyclosporin, tacrolimus, rifampicin, phenobarbital, phenytoin, carbamazepine and verapamil*	All patients with an active prescription of interacting drugs at the same time the DOAC was prescribed, were checked whether the DOAC or the interacting drug was discontinued and replaced by an alternative drug 24 hours after the start of the combination. Patients treated with verapamil and dabigatran at the same time, were checked whether the dose of dabigatran was adjusted.	Dutch national G-standard [18] SmPC DOAC [20]
2b. Rivaroxaban versus renal function	All patients treated with rivaroxaban, were checked whether the dose of rivaroxaban was adjusted based on the renal function.	Dutch national G-standard [18] SmPC Rivaroxaban [21]
2c. Dabigatran versus renal function and age	All patients treated with dabigatran were checked whether the dose of dabigatran was adjusted based on the renal function and patient age.	Dutch national G-standard [18] SmPC Dabigatran [22]
2d. Apixaban versus serum creatinine, body weight and Age	All patients treated with apixaban were checked whether the dose of apixaban was adjusted based on the serum creatinine, body weight and patient age.	Dutch national G-standard [18] SmPC Apixaban [23]
3. LMWH versus renal function and bodyweight	All patients treated with therapeutic doses of tinzaparin or nadroparin were checked whether the doses of the LMWHs were adjusted based on the renal function and patient body weight.	EMC: Vademecum hematology [24] & Dutch national G-standard [18] RdGG: SmPC tinzaparine [25] & Dutch national G-standard [18]
4. Pre-operative INR value	All patients undergoing surgery using VKAs, were checked whether the pre-operative INR value 24 hours before surgery was adequate. The cut-off pre-operative INR value was based on the bleeding risk of the surgical procedure: high (INR ≤ 1.5), low (INR ≤ 2.0), and clinically non-relevant bleeding risk (INR ≤ 3.0).	Pre-operative cut-off INR values (ACCP guideline) [26]

VKA Vitamin K antagonist, *DOAC* Direct Oral Anticoagulant, *LMWH* Low Molecular Weight Heparin, *SmPC* Summary of Product Characteristics, *EMC* Erasmus University Medical Center, *RdGG* Reinier de Graaf Hospital, *INR* International Normalized Ratio, *ACCP* American College of Chest Physicians

were obtained by logistic regression analysis, with the time period (intervention period versus usual care period) as primary variable. In order to adjust for possible predictors, multivariable logistic regression analysis was performed. The following possible predictors were initially entered into the model: age, length of hospitalization, hospital type, surgery and treatment with VKAs, DOACs or LMWHs. Variables that changed the beta-coefficient with more than 10% were retained in the model. Adjusted odds ratios (ORadj) and 95% confidence intervals (95% CI) were reported.

RESULTS

Study population

During the study period 2,577 patients were eligible for inclusion. In 677 patients, at least one reason for exclusion was present. Fourteen patients withdrew their consent after signing the informed consent due to medical reasons. Thus, in total 1,886 patients were included in our analysis, which included 941 patients in the usual care period and 945 patients in the intervention period (Figure 1). Characteristics of the included patients are presented in Table 2. Of these, the majority in both groups were male and the median age was 69 years. There were no differences between the two groups in gender, age, prior thrombotic event, hospital type, weight, renal function and high and low bleeding risk of the surgical procedure (in cases where the patients had to undergo surgery).

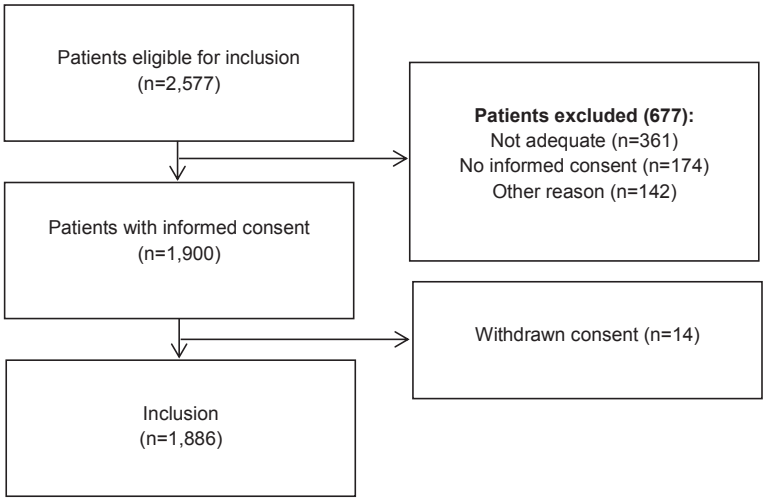

Figure 1. Study flow

Table 2. Baseline characteristics of the patients

Characteristic	Usual care period (*n*=941)	Intervention period (*n*=945)	p-value
Male gender	562 (59.7)	578 (61.2)	0.522
Age, years	69 [59-77]	69 [59-77]	0.665
Length of hospitalization, days	8 [5-14]	7 [3-13]	**< 0.001**
Prior bleeding	198 (21.0)	269 (28.5)	**< 0.001**
Prior thrombotic event	448 (47.6)	461 (48.8)	0.610
Hospital type, University Medical Center	472 (50.2)	472 (49.4)	0.927
Weight	80 [70-91]	80 [70-93]	0.177
e-GFR, ≤50 ml/min/1.73m^2	301 (33.0)	266 (30.1)	0.189
Surgery	340 (36.1)	330 (34.9)	0.583
Bleeding risk surgical procedure			
High bleeding risk	243 (25.8)	212 (22.4)	0.085
Low bleeding risk	57 (6.1)	62 (6.6)	0.653
Clinically non-relevant bleeding risk	40 (4.3)	60 (6.3)	**0.032**
Type of anticoagulant therapy*			
Vitamin K antagonist	646 (68.7)	553 (58.5)	**< 0.001**
Direct oral anticoagulant	80 (8.5)	263 (27.8)	**< 0.001**
Low-molecular-weight-heparin	488 (51.9)	423 (44.8)	**0.002**

Figures in bold are statistically significant.
Results are presented as median [interquartile range] or as number of patients (%) for non-continues data. N, number of patients at risk; *e-GFR* estimated glomerular filtration rate.
*Patients can use multiple anticoagulants during hospitalization.

Patients included in the intervention period had a shorter hospital stay (p <0.001), had more prior bleeding events (p <0.001) and a larger number of patients had a surgical procedure with a clinically non-relevant bleeding risk (p= 0.032). The use of VKAs (p <0.001) and LMWHs (p= 0.002) was less in patients in the intervention group but the use of DOACs was higher (p <0.001).

Adherence to anticoagulant guidelines

Table 3 shows the proportions of the admitted patients in which the prescribing physician adhered to one or more of the anticoagulant guidelines. Logistic regression analysis revealed that the overall adherence was significantly higher in the intervention period [75.3% (497/660)] compared to the usual care period [63.4% (395/623)] (odds ratio [OR] 1.76, 95% confidence interval [95% CI] 1.38-2.24). After adjustment for the possible predictors (i.e. age, length of hospitalization, hospital type, surgery and treatment with

VKAs, DOACs or LMWHs), the adjusted OR was 1.58 (95% CI 1.21-2.05). As shown in Table 3, the significantly higher overall adherence in the intervention period was attributed to dosing of LMWHs in relation to renal function and bodyweight. The odds ratio was 1.58 (95% CI 1.16-2.14). The other guidelines (drug-drug interactions in patients using VKAs, perioperative bridging of anticoagulants and dosing of DOACs) showed no significant differences between the usual care period and intervention period.

The proportions of the prescriptions in which the prescribing physician adhered to each of four anticoagulant guidelines occurred in 569 out of 811 (70.2%) prescriptions in the usual care period and in 657 out of 834 (78.8%) prescriptions in the intervention period. After adjustment for the same possible predictors, the adjusted odds ratio was 1.42 (95% CI 1.12-1.80).

Table 3. Adherence of prescribing physicians to guidelines based on prevailing anticoagulant therapy protocols

		Adherence		
		Usual care period (*n*=941)	**Intervention period (*n*=945)**	**OR [95% CI]**
1.	VKA and interacting drugs	103/111 (92.8%)	74/81 (91.4%)	0.82 [0.29-2.36]
2.	DOAC and interacting drugs, renal function, age and body weight	69/80 (86.3%)	228/263 (86.7%)	1.04 [0.50-2.15]
3.	LMWH versus renal function and bodyweight	217/393 (55.2%)	204/309 (66.0%)	**1.58 [1.16-2.14]**
4.	Pre-operative INR value	180/227 (79.3%)	151/181 (83.4%)	1.31 [0.80-2.18]
	Overall adherence	395/623 (63.4%)	497/660 (75.3%)	**1.76 [1.38-2.24]**
				1.58[a] [1.21-2.05]

Figures in bold are statistically significant.
OR odds ratio, *95% CI* 95% confidence interval, *VKA* Vitamin K antagonist, *DOAC* Direct Oral Anticoagulant, *LMWH* Low Molecular Weight Heparin, *INR* International Normalized Ratio
[a]OR, adjusted for predictors (age, length of hospitalization, hospital type, surgery and treatment with VKAs, DOACs or LMWHs).

DISCUSSION

The overall adherence to anticoagulant guidelines was significantly higher after the implementation of a multidisciplinary antithrombotic team focusing on education, medication reviews, drafting of local anticoagulant therapy protocols, patient

counseling and medication reconciliation. The significantly higher overall adherence in the intervention period can be attributed to the improvement of dosing of LMWHs in relation to renal function and bodyweight.

Earlier multifaceted intervention studies also showed a positive impact on guideline and protocol adherence. Maynard et al. revealed that implementation of a multidisciplinary team, focusing on patients with identified VTE events and treated with warfarin or LMWHs led to improved inpatient anticoagulation and management of venous thromboembolism [15]. Bos et al. introduced an educational program for prescribers in the hospital combined with audit and feedback by the hospital pharmacist. This led to a significant decrease in non-adherence from 30.5 to 21.8% of prescribing physicians to key pharmacotherapeutic guidelines, such as gastric protection in case of use of NSAID in hospitalized surgical patients and perioperative bridging of antithrombotics [14]. Other multifaceted intervention studies focusing on antibiotics found an increase in the rate of guideline adherence of antibiotic prescription [27, 28]. The hypothesis that a multifaceted approach is the most effective method to improve protocol adherence is supported by a previous study of Worel et al. who described that lack of audit tools and feedback systems and the presence of an abundance of guidelines with conflicting recommendations result in lack of guideline adherence [11]. Furthermore, passive dissemination of guidelines alone is often insufficient to have a positive impact on guideline adherence [13]. This study shows that the implementation of a multidisciplinary antithrombotic team leads to a significant increase in adherence to anticoagulant guidelines, specifically dosing of LMWHs. The improvement was obtained on top of other measures as medication surveillance by hospital pharmacists and clinical rules, which were part of usual care. Furthermore, active strategies such as education and medication reviews are needed to increase the knowledge and skills of prescribing physicians and thereby improve the adherence of guidelines. Comparing the different intervention studies on protocol adherence with each other is difficult given that the interventions in the various studies differ from each other. Moreover, this study focused on anticoagulant guidelines including patients treated with VKAs and DOACs while other studies focused mainly on patients treated with warfarin or LMWHs for specific indications, such as VTE. The significant increase in the number of DOAC users during the intervention period compared to the usual care period may be explained with as in 2016 (at the time of the intervention period) DOACs have been recommended as the first choice treatment of VTE [29].

The majority of overall adherence to anticoagulant guidelines was mainly caused by the improvement of dosing of LMWHs (OR 1.58 [95% CI 1.16-2.14]). Slikkerveer et al. found that most prescribing errors with LMWH treatment included overdosages and

underdosages that were not correctly adjusted to body weight or renal function [30]. The significantly higher adherence to dosing of LMWH therapy in the intervention period may be explained by the fact that during the intervention period medication reviews were performed by hospital pharmacists with attention paid to both bodyweight and renal function in relation to the dose of LMWHs. This differs from the usual care period where attention was only paid to the renal function in relation to dosing of LMWHs. Focusing on both body weight and renal function may have led to the improvement of dosing of LMWHs among prescribing physicians. LMWHs are one of the most frequently therapeutically prescribed anticoagulants in hospitalized patients. Besides, as dosing is based on both bodyweight and renal function, prescribing errors occur frequently. This may have contributed to the fact that the greatest effect of the hospital-based multidisciplinary antithrombotic stewardship was seen on dosing of LMWHs. Guidelines concerning drug-drug interactions in patients using VKAs and DOACs, perioperative bridging of anticoagulants and dosing of DOACs in relation to renal function, age and bodyweight showed no significant association in adherence of prescribing physicians after the implementation of a multidisciplinary antithrombotic team. A possible explanation is that during the usual care period the pharmacy software automatically checked the prescribed medication in relation to the medication record that was available within the pharmacy system and automatically generated medication surveillance and signals in case of interactions, overdose, duplications and contraindications. In addition, the pre-operative INR value before surgery was already closely monitored by the physician during the usual care period. Despite the significant increase in adherence to anticoagulant guidelines in this study, 24.7% of the prescribing physicians were non-adherent to the anticoagulant guidelines after implementation of the multidisciplinary antithrombotic team. Although this study showed that the implementation of a multidisciplinary antithrombotic team leaded to a significant increase in adherence to anticoagulant guidelines, there still may be room for improvement.

Strengths and limitations

To our knowledge, this is the first study describing the effect of hospital-based multidisciplinary antithrombotic stewardship on the adherence to anticoagulant guidelines among prescribing physicians. Furthermore, the study was performed in two different types of hospitals, a University Medical Center and a general teaching hospital, which increases the generalizability of our findings. Another strength of this study is the multifaceted approach which combines different interventions to improve the adherence to anticoagulant guidelines.

This study has several limitations. First, seven guidelines derived from several anticoagulant therapy protocols were selected. This is a limited set of anticoagulant guidelines and may not be generalizable to all anticoagulant protocols. A second limitation is that the cost-effectiveness of the intervention has not been analyzed. Additional costs were incurred by performing medication reviews, which were conducted by the hospital pharmacist. Furthermore, drafting of local protocols and education to physicians and nurses were performed by healthcare providers, such as a specialized thrombosis nurse, a hematologist, a hospital pharmacist, and a cardiologist. Third, logistic regression analysis doesn't take into consideration any clustering within prescriber (e.g. surgical versus medical). Fourth, this study is a prospective non-randomised before-and-after study, without a retrospective control group. Improvements may already have been implemented during the usual care period. Finally, the intervention is multifaceted making it difficult to say which specific intervention (e.g. medication reviews) has been of the greatest influence on improvement of anticoagulant therapy protocol adherence among prescribing physicians**.**

CONCLUSION

This study showed that introduction of hospital-based multidisciplinary antithrombotic stewardship resulted in a significantly higher overall adherence to anticoagulant guidelines among prescribing physicians, mainly based on the improvement of correct dosing of low-molecular-weight-heparins. Future studies should focus whether higher adherence to anticoagulant guidelines contributes to improvement in clinical outcomes.

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Supplementary Table 1. Data collection

Part	Data content
Patient data	Patient ID
	Date of birth
	Gender
	Weight on the day of hospitalization
	Date of hospitalization
	Date of hospital discharge
	Type of hospital (University Medical Center/general teaching hospital)
	Bleeding in history (yes/no)
	Thrombotic event in history (yes/no)
Interventions	Surgical procedure (yes/no)
	If surgical procedure, bleeding risk of the surgical procedure (high, low, or clinically non-relevant) [17]
Medication data	Type of anticoagulant therapy
	• Vitamin K antagonist • Direct oral anticoagulant • Low-molecular-weight-heparin
Clinical chemistry data	Laboratory values
	• e-GFR (ml/min/1.73m^2) on the day of hospitalization • INR

e-GFR estimated glomerular filtration rate, *INR* International Normalized Ratio

Chapter 8

General Discussion

Anticoagulants are frequently used drugs in the prevention and treatment of thromboembolic diseases [1,2]. Atrial fibrillation (AF), acute myocardial infarction (MI), ischemic stroke and venous thromboembolism (VTE) are the most common indications for treatment with anticoagulant therapy [3]. Over the last decades the number of patients on anticoagulants has increased to more than 500,000 in the Netherlands [4]. Although anticoagulants are highly effective, they are also carrying a significant bleeding risk [5-7]. On the other hand, some patients still develop thrombosis despite being treated with anticoagulants [8]. Due to these risks and the increasing demand for anticoagulants, optimizing anticoagulant therapy is important.

The main aim of this thesis was to study the implementation of antithrombotic stewardship on the efficacy and safety of anticoagulant therapy during and after hospitalization. First, we studied determinants of an increased INR and of bleeding complications in hospitalized patients. In addition, the proportion of anticoagulant medication error reports in Dutch hospitals and in primary care was determined. We designed an interrupted time series study to determine the effect of antithrombotic stewardship consisting of multiple interventions on the occurrence of thrombotic and bleeding events. Finally, we performed a study focusing on the effect of antithrombotic stewardship on adherence to anticoagulant guidelines among prescribing physicians.

In this final chapter our main results are reviewed in a wider perspective in relation to the current literature and the main objectives of this thesis.

DETERMINANTS OF BLEEDING

Clinical prediction models are developed to predict outcomes of diseases and/or treatments for individual patients. Application of prediction models enables the identification of high risk patients and can assist in choosing the optimal treatment. In chapter 2, we developed and validated a clinical prediction model for the risk of an INR ≥ 4.5 in patients admitted to medical or surgical wards who are treated with vitamin K antagonists (VKAs). This model was based on risk factors that are electronically collected during routine care [9]. The prediction model can help physicians in identifying patients with a high risk of bleeding during VKA therapy. Using the prediction model may also aid in counselling and informing patients about their potential risk of bleeding while using anticoagulants, including identifying patients who might benefit from more careful management of anticoagulation. Existing prediction models for bleeding events in patients using VKAs are not applicable to electronic clinical decision support systems ('clinical rules') since the risk factors are not easily extractable from electronic medical

records (EMRs). Furthermore, existing prediction models do not concern the general hospital population [10,11]. In the validation cohort of our study, the predictive value of the model for an INR ≥ 4.5 in hospitalized patients using vitamin K antagonists was 0.71, meaning the prediction model is applicable to patients that were hospitalized in a different time period than that of our development cohort.

Adding more variables (e.g. information on the indication of the VKA or comorbidities of the patient) should be taken into account in future studies in order to increase the performance of the model. However, data from electronic medical records (EMRs) are mainly stored in unstructured free text, which makes it impossible to extract the data efficiently and accurately. Therefore, a more structured documentation of data in the EMR is needed. Future studies should investigate whether implementation of the prediction model as an electronic clinical decision rule leads to a reduction in the number of inpatients with an INR ≥ 4.5 and whether this results in less bleeding events.

In our study mentioned above, we used an INR ≥ 4.5 as a surrogate marker for an increased risk of bleeding. This is an adequate marker because 4.5 is the INR at which the risk of bleeding increases sharply [12]. However, using surrogate endpoints like the INR instead of the real clinical outcome is less accurate [13]. Therefore, in chapter 3, we determined the prevalence and potential risk factors of the clinical endpoint bleeding in anticoagulant users during hospitalization. We found a prevalence of in-hospital bleeding events in patients using anticoagulant therapy of 7.2% (65 out of 906 patients). The majority of bleeding events occurred in surgical patients. Female gender, both high-and low-bleeding-risk surgical procedures and non-surgical interventions were identified as determinants for these bleeding events. Part of the increased risk of bleeding in surgical patients may be explained by the temporarily discontinuation and/or bridging of anticoagulants in the perioperative period. At the time of our study, the majority of VKA-treated patients with a high risk of a thrombo-embolic event were bridged with therapeutic doses of low-molecular-weight-heparins (LMWHs) or unfractionated heparin before and after surgical interventions [14,15]. Several studies have shown that patients who receive bridging anticoagulation therapy have an increased risk of overall and major bleeding events in the peri-procedural period [16,17]. Because of these findings, the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial was designed to investigate whether bridging anticoagulation is necessary for patients with atrial fibrillation, who need an interruption in warfarin treatment for elective surgery or other elective invasive procedure. They found that no bridging anticoagulation was non-inferior to perioperative bridging with LMWH for the prevention of arterial thromboembolism and that forgoing bridging treatment

also decreased the risk of major bleeding compared to perioperative bridging with LMWH [18]. This resulted in a change of Dutch guidelines, where bridging is no longer advised in patients with a CHA2DS2-VASc score of ≤ 8 [19]. Implementation of these new bridging guidelines in hospitals took place after the study mentioned above.

In order to reduce periprocedural complications, several initiatives have been carried out to improve perioperative safety. The Dutch guideline on integrated antithrombotic care ('Landelijke Standaard Ketenzorg Antistolling'; LSKA), published in August 2014, stated a shared responsibility of surgeon and anesthesiologist concerning continuing, temporarily discontinuing and/or bridging of anticoagulants in the preoperative period [20]. In addition, van Fessem et al. performed a quality-improvement project at the anesthesiology department of the Erasmus University Medical Center to improve perioperative safety. The quality improvement consisted of distribution of education materials, development of a guideline based protocol, education meetings for physicians and physician assistants, and adjustments in EMR creating a more clearly defined plan regarding continuing, temporarily discontinue and requirement of bridging therapy. It resulted in a significant (51%) increase in safe, guideline based, preoperative plans for patients using VKAs [21]. Since in our study the large majority of bleedings occurred in association with surgical or other invasive procedures, future studies should focus on the comparison of bleeding events occurring in patients on anticoagulant therapy and in patients without anticoagulant therapy in relation to surgery or invasive procedures. This makes it possible to determine to what extent bleeding events are caused by the surgical procedure itself.

Our studies aimed to predict the risk of bleeding in hospitalized patients. On the one hand by using INR as an indicator for an increased risk of bleeding in adult patients who are treated with VKAs, based on risk factors that are electronically collected during routine care. On the other hand to determine potential other risk factors of bleeding in anticoagulant drug users during hospitalization. Future studies should combine the risk factors from both studies to develop models predicting a possible increasing risk of bleeding in hospitalized patients on VKA therapy. In addition, clinical prediction models of thrombotic events should be developed and future studies should focus on the development of prediction models for bleeding events in patients using direct oral anticoagulants (DOACs). A prediction model may offer support in making early treatment decisions, leading to a more efficient healthcare service.

MEDICATION ERRORS WITH ANTICOAGULANTS

In a study reported in chapter 4, we have shown that anticoagulant medication error reports concern 8.3% (3,557 error reports out of 42,962) of all medication errors reported to the Central Medication incidents Registration (CMR) reporting system between December 2012 and May 2015 [22]. Medication errors derived from internal reporting systems in hospitals and community pharmacies in the Netherlands are reported through a web-based CMR reporting form. The CMR is a Dutch nationwide online registration system for medication error reports and is based on anonymous self-reports of medication errors by all caregivers [23]. Our study revealed that anticoagulants were found to be frequently involved in medication error reports. Similar percentages of anticoagulant-related medication errors have also been reported in previous studies [24,25]. In addition, we found that LMWHs, which are frequently used as prophylaxis to prevent thrombosis, were most often reported as a causative agent and that especially the prescribing and administering phases were involved in anticoagulant errors. These insights obtained from our study can be used to provide targeted interventions to minimize the number of anticoagulant medication error reports.

Some limitations regarding the methodology of the study should be mentioned. First, reporting of medication errors to the CMR reporting system is voluntary. Voluntary reporting systems will suffer from underreporting, selective reporting and incomplete reporting of medication errors [26]. For instance, caregivers are inclined to report the more serious medication errors, leading to an incomplete overall picture of the reported medication errors [27]. Furthermore, in 98.2% of medication error reports in our study, the consequences for the patient of the error were not reported and can therefore not be evaluated. In addition, the majority of medication errors were reported by hospitals (hospital pharmacists, physicians, nurses). A proven strategy improving the reporting rate of medication errors is to ensure there is a dedicated person who is responsible for the reporting of medication errors [28-30]. This dedicated individual may be trained in reporting medication errors and can ensure that the information regarding the reported medication errors to the CMR is complete. Medication errors can be reported to the CMR reporting system through a web-based CMR reporting form, which is a time consuming method. A more efficient method enhancing the quality and reporting rate of the reports would be a direct link between the EMR and the CMR reporting system. Introducing such a system makes it possible to produce a report from the EMR after which it can be directly sent to the CMR.

ANTITHROMBOTIC STEWARDSHIP

In chapter 5, we described the design of the antithrombotic stewardship study: a multidisciplinary team approach towards improving antithrombotic therapy outcomes during and after hospitalization. The best method for evaluating the efficacy of intervention on patient safety is by using a cluster randomized controlled design [31,32]. We could have used a clustered design, in which the hospitals (University Medical Center vs. general hospital) were the units of randomization. However, the main disadvantage with this design is that large sample sizes would be needed to account for the intracluster correlation in the hospital, which would be costly. Another disadvantage of this method is the comparability of the clusters due to existing differences in patient population between a University Medical Center and a general hospital. For the antithrombotic stewardship study, as for many other safety interventions, a regular randomized controlled design on patient level is considered not feasible. Due to the multifaceted approach of the intervention, contamination of the control group due to receiving parts of the intervention would occur. Moreover, we hypothesized that implementation of the multidisciplinary team contribute to patient safety, making it less ethical to randomize the intervention to a selected group of patients in the hospital. When a randomized controlled design is not suitable, an alternative study design, in order of methodological strength, is a stepped wedge design. In a stepped wedge design the intervention is sequentially rolled-out over clusters and clusters are their own controls [33]. Due to high costs for the large amount of resources needed, a stepped wedge design was not feasible for us [34]. For the antithrombotic stewardship study we have chosen to use a prospective non randomized before-after design with an interrupted time series analysis. The major advantages of this design are the practical aspects and the lower implementation costs. In addition, the interrupted time series analysis enables to evaluate the longitudinal effect of the intervention and adjusts for trends [35], which contributes to a more robust design when compared to a simple pre-post design. However, effects could still be attributed to developments other than the intervention.

Besides the fact that the majority of reported intervention studies are uncontrolled before-after studies, most studies focused on surrogate endpoints such as compliance to antithrombotic protocols and transitioning of patients on anticoagulation to outpatient management [36-38]. We collected data on a large patient cohort, making it possible to study clinically relevant endpoints: bleeding and thrombotic events during hospitalization and until three months after hospitalization as primary outcome. All-cause mortality, length of hospitalization and medical costs were secondary outcomes. However, several challenges were encountered when collecting clinical outcomes. Data

on bleeding and thrombotic events occurring during hospitalization were derived from reports of the responsible physicians documented in the EMR. Post discharge data were collected from reports from general practitioners, thrombosis services and/or patients themselves. Therefore the collected data are dependent on the information recorded by the responsible physician, general practitioner or patient, which may lead to underreporting of the number of bleeding and thrombotic events, especially the non-major bleeding events. Future research should investigate the proportion of underreporting of bleeding and thrombotic events in anticoagulant users and strategies must be developed to ensure that underreporting decreases. Proactive information on reporting of bleeding and thrombotic events by caregivers and educational interventions in patients may help to improve reporting rates.

Effect of the multifaceted intervention

To improve the effect and safety of antithrombotic therapy during and after hospitalization, we have chosen a multifaceted approach by introducing a multidisciplinary antithrombotic team focusing on education of physicians, nurses and hospital pharmacists, medication reviews by hospital pharmacists focusing on optimizing treatment with anticoagulants, drafting of local anticoagulant therapy guidelines, patient counseling and medication reconciliation at admission and discharge. In chapter 6, we have shown that introduction of the multidisciplinary antithrombotic team had a profound effect on the proportion of patients with bleeding and thrombotic events from hospitalization until three months after hospitalization. Furthermore, implementation of a multidisciplinary appeared to result in lower all-cause mortality. The improvement in the effect and safety of antithrombotic therapy in our study has been achieved through a multifaceted approach consisting of several interventions. The impact and recommendations regarding the safety interventions will be reviewed in more detail below.

Education of healthcare providers

Studies in which education was part of a multifaceted intervention showed efficacy on prescription errors and potential adverse drug events [39-42]. Moreover, Kroll et al. showed that face-to-face education led to positive effects on the quality of prescribing [43]. However, further strategies should be considered to optimize education to healthcare providers. Introducing e-learning modules may increase the knowledge of antithrombotic therapy. A previous study on the effect of e-learning on prescribing of medication showed that a short e-learning intervention significantly improved the prescribing skills of junior doctors [44]. Our hypothesis is when e-learning modules on antithrombotic therapy are made compulsory at the start of employment, knowledge

of antithrombotic therapy among physicians, nurses and hospital pharmacists increases and when the modules are repeated periodically they may have a sustained effect on knowledge.

Medication reviews by hospital pharmacists

Medication reviews by hospital pharmacists have been used to improve the quality of prescriptions by physicians. However, performing medication reviews in daily practice is time-consuming. To make the efforts of the hospital pharmacist regarding medication reviews more efficient, the following recommendations are made. First, application of risk prediction tools, as described in chapter 2 and 3, enable the identification of high risk patients who would benefit most from medication reviews. Of course, additional risk prediction models should be developed, in order to not only predict patients at risk of bleeding, but also at risk of thrombotic events. Second, implementation of clinical rules regarding antithrombotic therapy instead of the conventional medication surveillance by hospital pharmacists increases the efficiency. Clinical rules could focus on dosing of LMWHs (i.e., in relation to decreased renal function and bodyweight), double and triple antithrombotic treatment [45] and perioperative bridging of anticoagulants. Third, detailed information on antithrombotic therapy (e.g. start date of triple therapy and indication) from the patient's medical record is required for performing medication reviews. In many cases, this information is poorly retrievable or completely untraceable. A more structured documentation is needed to make it possible to develop such clinical rules. Fourth, medication reviews were performed focusing on dosing (i.e., in relation to decreased renal function, bodyweight and age), duplicate medication, drug–drug interactions, contraindications and perioperative bridging of anticoagulants. Future studies should investigate whether additional aspects should be included in the medication review, such as reversal of anticoagulation and monitoring of potential side effects or adverse events and medication adherence to treatment with anticoagulant therapy.

Anticoagulant therapy guidelines

In chapter 7, we described the results of a study designed to determine the effect of hospital-based multidisciplinary antithrombotic stewardship on adherence to anticoagulant guidelines among prescribing physicians [46]. Adherence to anticoagulant guidelines was assessed by using prevailing anticoagulant therapy guidelines which are implemented in the local hospital protocols. Seven relevant guidelines derived from several anticoagulant therapy protocols were selected, such as drug-drug interactions in patients using VKAs, dosing of LMWHs in relation to renal function and bodyweight and perioperative bridging of anticoagulants.

Introduction of hospital-based multidisciplinary antithrombotic stewardship focusing on education, medication reviews, drafting of local anticoagulant therapy protocols, patient counseling and medication reconciliation at admission and discharge led to a significantly higher overall adherence to anticoagulant guidelines among prescribing physicians, mainly based on the improvement of correct dosing of LMWHs in relation to renal function and bodyweight. An electronic clinical decision support rule ('clinical rule') combining renal function and bodyweight of the patient with the prescribed LMWH would be useful to improve the quality of prescribing. 24.7% of the prescribing physicians were still non-adherent to the anticoagulant guidelines after implementation of the multidisciplinary antithrombotic team. This was mainly attributed to dosing of LMWHs. Inconsistency between international and even national guidelines on dosing of LMWHs in relation to renal function could be a possible reason [19,47]. For instance, existing discrepancies between guidelines on dosing of LMWHs in patients with renal insufficiency for treatment of cancer-associated thrombosis [48,49]. Another explanation is that many physicians question the clinical relevance of adjusting the dose of LMWHs in relation to renal function as a result of which they consciously deviate from the guidelines. Physician adherence to other guidelines was quite high (VKA and interacting drugs: 91.4%; DOAC and interacting drugs, renal function, age and body weight: 86.7%; pre-operative INR value: 83.4%) after implementation of the multidisciplinary antithrombotic team. Besides introduction of a clinical decision rule on LMWH dosing, another possible intervention may be to incorporate the adherence results into the educational programs in order to provide feedback to the prescribing physicians. Furthermore, Moesker et al. revealed inconsistencies between guideline recommendations for venous thromboembolism prophylaxis and possible barriers for the guideline implementability [50]. Introducing guideline developers, focusing on the quality, consistency and readability of guidelines, may improve implementability of guidelines resulting in higher adherence to guidelines.

Patient counseling

Studies on the impact of patient empowerment showed positive effects on health outcomes, patient satisfaction, self-efficacy and adherence [51-54]. Empowered patients understand their health conditions, are more satisfied and have a higher self-efficacy [51]. In our study, a dedicated thrombosis nurse was responsible for patient empowerment. During hospital stay, patients were asked to participate in the empowerment program. In a session of approximately 30 minutes information and education regarding anticoagulant therapy to patients was provided.

We observed that, given the large number of patients treated with anticoagulant therapy, one designated person in our hospital was insufficient to empower each hospitalized patient on anticoagulant therapy. Therefore, further interventions should be considered to optimize patient empowerment and to make it more efficient. One way is to deploy trained hospital pharmacy assistants in the empowerment of patients on anticoagulant therapy during medication reconciliation at hospital admission. Another way to enhance patient empowerment is by using technology as discussed by Calvillo et al. [55]. One of the practical approaches to empower patients is by using computer-based games designed for training purposes. Using such technologies may optimize the empowerment of patients treated with anticoagulant therapy.

Medication reconciliation

Multiple studies have shown that drug-related problems can be prevented with medication reconciliation [56-58]. We performed medication reconciliation by providing continuity of pharmaceutical care focusing on anticoagulant therapy. At admission, data from the patient's thrombosis service regarding dosing schemes, indication of anticoagulation, type of VKA, INR measurements and the INR target ranges were handed over to the responsible physician. At discharge, pharmacotherapy advices from the medication reviews were handed over to either the thrombosis service or the general practitioner, and to the community pharmacist. Privacy constraints in the Netherlands prohibit the use of one computer software program that is accessible to all healthcare providers and pharmacists inside and outside the hospital. This makes medication reconciliation complex and time-consuming. Development of a link between the various information systems of the healthcare providers would be useful to easily exchange data from the patient and to decrease administrative tasks. Engaging patients in the responsible management of their own healthcare process by the use of eHealth would be another option for optimization of medication reconciliation.

CONCLUSIONS

Summarizing, our results show that a multifaceted approach with a range of interventions, such as the interventions described above, contributes to patient safety. In this study we have chosen a multifaceted approach by combining different interventions since multiple interventions would address barriers at different levels changing health-care professional behaviors [59,60]. Despite the fact that multifaceted interventions require more resources [61], our study showed that implementation of a multidisciplinary antithrombotic team improved the safety of antithrombotic therapy.

FUTURE ORGANIZATION OF ANTITHROMBOTIC HEALTHCARE

In this thesis we focused on improving the efficacy and safety of anticoagulant therapy during and after hospitalization by implementation of a multidisciplinary antithrombotic team. In addition, other organizational measures regarding antithrombotic therapy could contribute to patient safety. Recently, the report "Time to connect" (Tijd voor verbinding) has been published in the Netherlands. The aim is to further reduce potential preventable harm and mortality in hospital care [62]. The report stresses the importance of providing optimal care to patients on antithrombotic therapy focusing on real-time availability of medication data between hospitals and primary care, increasing the knowledge and expertise regarding antithrombotic therapy and professionalization of the registration of incidents and complications. Other possible initiatives improving the efficacy and safety of anticoagulant therapy will be discussed below.

DOACs have been approved over the last years for several different indications such as atrial fibrillation and venous thromboembolism [63]. Considering the high prevalence of renal insufficiency in elderly patients and since most patients requiring DOACs are older, it is important to evaluate the renal function before starting treatment and also periodically during the therapy with DOACs, as DOACs can accumulate and potentially increase the bleeding risk in patients with renal insufficiency. In patients with impaired liver function DOACs should be prescribed with caution as well. These patients have not been included in the large registration studies. Furthermore, compared with warfarin, there is a higher risk of gastrointestinal bleeding in high-dose dabigatran (150 mg b.i.d), rivaroxaban and high-dose edoxaban (60 mg daily) [64] and drug-drug interactions must still be considered with the use of DOACs [65]. To ensure safe use of these drugs, clarity regarding the tasks and responsibilities is needed.

The multidisciplinary antithrombotic team consisting of caregivers from hospitals and primary care could play an important role in the treatment and monitoring of DOAC users. Routine kidney and liver function monitoring, switching from VKA to a DOAC and vice versa, education to patients and the registration of complications of treatment with DOACs are examples of tasks where the multidisciplinary antithrombotic team can make an important contribution to the safe use of DOACs.

Another strategy for optimization of monitoring and management of anticoagulant therapy could be by involving multidisciplinary antithrombotic teams in dosing of VKAs in hospitalized patients. Hospitalized VKA patients may be at increased risk of bleeding, for example because of perioperative bridging of anticoagulation therapy and start of additional medication influencing the metabolism of anticoagulants [17,66]. Information

on previous dosing schemes of patients are lacking, and on top of that, the majority of anticoagulants are prescribed by junior doctors who are relatively inexperienced [67,68]. The multidisciplinary antithrombotic team may offer consultation services for the dosing of VKAs in hospitalized patients and can be made responsible for adequate transitioning of patients from the inpatient to the outpatient setting and vice versa.

FUTURE PROSPECTS AND RECOMMENDATIONS

The studies presented in this thesis has enriched our knowledge on risk of bleeding in hospitalized patients and on anticoagulant medication errors. Furthermore, we have demonstrated the important role of antithrombotic stewardship on the efficacy and safety of anticoagulant therapy during and after hospitalization. The findings of the studies described in this thesis have led to the following recommendations for clinical practice and suggestions for future research.

Recommendations for clinical practice

- Clinical prediction models for the risk of an INR ≥ 4.5 in hospitalized patients on VKA therapy should be introduced in daily clinical practice. Application of prediction models enables the identification of high risk patients and may assist in the treatment decision-making process. In addition, clinical prediction models for thrombotic events should be developed.
- A multidisciplinary antithrombotic team focusing on education, medication reviews by hospital pharmacists, drafting of local anticoagulant therapy guidelines, patient counseling and medication reconciliation at admission and discharge increases the effect and safety of antithrombotic therapy. Furthermore, lower all-cause mortality and higher overall adherence to anticoagulant guidelines were observed. Multidisciplinary antithrombotic teams should become a core service in hospitals.
- Introducing a clinical rule, based on one nationally adapted guideline, combining the renal function and bodyweight of the hospitalized patient with the prescribed LMWH could be useful to further improve adherence.
- Improvement in information technology is needed to easily exchange data on medication use between the various information systems of the healthcare providers.
- Expanding the role of the multidisciplinary antithrombotic team by monitoring the treatment of DOAC users and through involvement in dosing of VKAs in hospitalized patients, is recommended.

Suggestions for future research

- Whether implementation of a clinical prediction model predicting the risk of an INR ≥ 4.5 during hospital stay, for adult patients who are treated with VKAs leads to a reduction in the number of bleeding events during hospitalization, should be investigated.
- Introduction of the multidisciplinary antithrombotic team had a profound effect on the proportion of patients with bleeding and thrombotic events from hospitalization until 3 months after hospitalization. Larger studies and studies with longer follow-up are needed to show specific effects per antithrombotic drug class or per hospital type.
- Further research should focus on which intervention(s) of the multifaceted approach had the most influence on the outcomes and which patients are at the highest risk and would benefit the most from implementation of the multidisciplinary antithrombotic team.

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Chapter 9

Summary

Anticoagulants are frequently used drugs for the prevention and treatment of thromboembolic diseases. Despite the clinical benefits, they are associated with a high risk of bleeding complications. Due to the risk of bleeding complications and the risk of thrombosis in patients not receiving adequate antithrombotic treatment or prophylaxis, optimizing anticoagulant therapy is important. We have performed several studies described in this thesis focusing on anticoagulant medication errors, determinants of an increased INR and of bleeding complications during hospitalization. In order to improve the efficacy and safety of anticoagulant therapy, we studied the effect of implementing a hospital-based multidisciplinary antithrombotic team.

The first part of this thesis focused on the determinants of an increased INR and of bleeding complications in hospitalized patients. In addition, the proportion of anticoagulant medication errors in Dutch hospitals and primary care was determined. In **chapter 1**, the scope, objective and outline of this thesis were described. Next, in **chapter 2**, we developed and validated a clinical prediction model for the risk of an INR ≥ 4.5 in patients admitted to medical or surgical wards who are treated with VKAs. Adult patients admitted to a tertiary hospital and treated with VKAs between 2006 and 2010 were analyzed. The study included 8,996 admissions of 6,073 individual patients treated with VKAs. We identified 1,507 admissions (17%) with an INR ≥ 4.5 during hospitalization in 1,112 individual patients. The final model included the following predictors for an INR ≥ 4.5: female gender, advanced age, concomitant medication (miconazole, cotrimoxazole, fluconazole, voriconazole, amiodarone and antithyroid drugs) and biochemical parameters: alanine amino transferase (ALAT), lactate dehydrogenase (LDH), albumin, estimated glomerular filtration rate (e-GFR) and C-reactive protein (CRP). In **chapter 3**, we determined the prevalence and potential risk factors of the clinical endpoint bleeding in anticoagulant users during hospitalization. We found that the prevalence of in-hospital bleeding events in patients using anticoagulant therapy was 7.2%; 95% CI 5.5–9.1 in all patients (65 out of 906 patients). Of the 65 patients with a bleeding event, 51 (78.5%) of these events were categorized as major bleeding and 14 (21.5%) as non-major bleeding. The median length of stay in patients with bleeding during hospitalization was 18 days (range of 8.5 to 34.5 days), and 7 days (range of 4 to 13 days) in patients without bleeding during hospitalization. Multivariate logistic regression analysis indicated that female gender (OR=2.1; 95% CI, 1.2-3.7), high-bleeding-risk surgical procedure (OR=5.3; 95% CI, 2.7-10.2), low-bleeding-risk surgical procedure (OR=4.9; 95% CI 1.9-12.6) and non-surgical interventions (OR=6.2; 95% CI, 3.0-12.6) were associated with bleeding in hospitalized patients treated with anticoagulants. In **chapter 4**, we assessed the proportion of medication error reports in hospitals and primary care in the Netherlands in which anticoagulants were involved. From December 2012 to May 2015, 42,962 medication errors were reported to the

Central Medication incidents Registration (CMR). Of these errors, 37325 (87%) originated from hospitals and 5637 (13%) from primary care. Anticoagulant medication errors were seen in 3557 reports out of a total of 42 962 (8.3%), of which 96% were reported by hospitals. A random selection of 1000 anticoagulant medication error reports revealed that low-molecular weight heparin was the most frequently reported medication class (56.2%) and that most reports concerned the prescribing phase of the medication process (37.1%). Furthermore, no difference in the proportion of reported anticoagulant medication errors were found before and after publication of the national guideline on integrated antithrombotic care.

The second part of this thesis focused on the effect of hospital-based multidisciplinary antithrombotic stewardship on the efficacy and safety of antithrombotic therapy during and after hospitalization. In **chapter 5**, we described the design of the antithrombotic stewardship study: a multidisciplinary team approach towards improving antithrombotic therapy outcomes during and after hospitalization. For the antithrombotic stewardship study we have chosen to use a prospective non randomized before-after design. Segmented regression analysis for the interrupted time series was used for analysis of the primary outcome (the proportion of patients with a composite end point consisting of one or more bleeding episode or one or more thrombotic event from hospitalization until three months after hospitalization), making it possible to evaluate the longitudinal effect of the intervention and to control for trends. In **chapter 6**, we studied the effect of implementing a hospital-based multidisciplinary antithrombotic team on the efficacy and safety of antithrombotic therapy during and after hospitalization. In total, 1886 patients were included of which 941 in the usual care period and 945 in the intervention period. The majority in both groups was male and the median age was 69 years. Introduction of the multidisciplinary team had no immediate impact +1.63% (-3.60% to +6.85%) on the proportion of patients with a composite end point consisting of one or more bleeding or one or more thrombotic events from hospitalization until three months after hospitalization, but over time the primary endpoint event rate decreased significantly with -1.83% (-2.58% to -1.08%) per 2 month period. All-cause mortality appeared to be reduced by the intervention (OR=0.71; 95% CI, 0.53-0.95). Medical costs per admission decreased by €790 (£685; $894) in the University Medical Center and €480 (£416; $544) in the general hospital, but this was not statistically significant. In **chapter 7**, we determined the effect of hospital-based multidisciplinary antithrombotic stewardship on adherence to anticoagulant guidelines by prescribing physicians. In the same study population as in chapter 6, adherence to anticoagulant guidelines was assessed by using prevailing anticoagulant therapy guidelines which are implemented in the local hospital protocols. Multivariable logistic regression analysis indicated that adherence was observed significantly more often during the intervention

period (OR=1.58; 95% CI 1.21-2.05). Detailed analysis identified that the significantly higher overall adherence in the intervention period was attributed to dosing of LMWHs (OR=1.58; 95% CI 1.16-2.14). Finally, in **chapter 8** we discussed the findings of the studies in this thesis and implications for clinical practice and recommendations for future studies on optimizing anticoagulant treatment were given.

Appendices

- Dankwoord
- List of co-authors
- PhD portfolio
- Curriculum Vitae

DANKWOORD

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PHD PORTFOLIO

	Year	Workload (ECTS)
1. General courses		
• Open Clinica training	2015	0.3
• CPO mini-course	2015	0.3
• Basic course on Regulations and Organization for Clinical Investigators (BROK)	2015	1.5
• Onderzoek dag 1 en 2 CORAZ (PUOZ)	2015	2.0
• Cardiologie (PUOZ)	2015	1.0
• Principles of epidemiologic data-analysis (NIHES)	2016	0.7
• Basic Introduction Course on SPSS	2016	1.0
• Pharmaco-epidemiology (NIHES)	2016	0.7
• Course Research Integrity	2017	0.3
• Biomedical English Writing Course	2017	3.0
• Methoden Klinisch Geneesmiddelen onderzoek	2017	1.0
2. Workshops		
• Trombosegame	2017	1.0
3. Conferences and presentations		
• Nationaal trombosecongres	2015	0.3
• Prisma Symposium, Amersfoort: *oral presentation*	2016	0.8
• Scientific Meeting Clinical Pharmacology Erasmus MC: *oral presentation*	2016	0.8
• Nederlandse Ziekenhuisfarmaciedagen: *oral presentation*	2016	0.8
• Wereldtrombosedag Reinier de Graaf Hospital: *oral presentation*	2017	0.8
• Nederlandse Ziekenhuisfarmaciedagen: *oral presentation*	2017	0.8
• LSKA congres, Utrecht	2017	0.3
• Regionale antistollingsbijeenkomst Erasmus MC	2017	0.8
• International Society for Pharmacoepidemiology, Montreal: *oral presentation*	2017	1.2
• FNT applicatiecursus: *oral presentation*	2018	0.8
• Wereldtrombosedag Erasmus MC: *oral presentation*	2018	0.8
• Nationaal trombosecongres	2018	0.3
• Masterclass Nationaal Nascholingscongres Anesthesiologie	2018	0.8
• Wetenschapsmiddag Reinier de Graaf ziekenhuis: *oral presentation*	2019	0.8

	Year	Workload (ECTS)
• European Hematology Association: *poster presentation*	2019	0.3
• International Society for Pharmacoepidemiology, Philadelphia: *oral presentation*	2019	1.2
4. Teaching		
• Education about anticoagulant medicines for hospital pharmacy assistants (2/year)	2017	0.8
• Education about anticoagulant medicines for general pharmacy assistants (2/year)	2017	0.8
• PUOZ Antistolling	2018	0.4
• Theoretical course on antihrombotic stewardship for Bachelor's student in medicine (2/year)	2018	0.8
5. Supervising of research projects of Master students		
• Sebnem Aybike Akgöl (Utrecht University) "The frequency of bleeding and thrombotic events in patients with antithrombotic treatment hospitalized in Reinier de Graaf Gasthuis: a descriptive pilot study"	2014-2015	2.0
• Lamyae Maanach (Utrecht University) "Risk factors of bleeding and thrombotic events during hospitalization"	2015-2016	2.0
• Jonathan Knikman (Utrecht University) "A comparison of quality of life, adherence and patient satisfaction between vitamin K-antagonist users and novel oral anticoagulant users"	2016	2.0
• Vera Bukkems (Utrecht University) "Vitamin K antagonist therapy: not a one-man job"	2016-2017	2.0
• Jennifer Hollander (Utrecht University) "Adherence to anticoagulant protocols"	2016	2.0
• Krishnika Jeyasimman (Utrecht University) "The effectiveness of antithrombotic related medication reviews: a pilot study"	2015-2017	2.0
• Shamayel Mobayyen (Utrecht University) "Accuracy of patient self-report of bleeding and thrombotic events 3 months after hospitalization"	2017	2.0
• Halat Naby (Utrecht University) "Antithrombotic stewardship: a pilot study"	2017	2.0
• Pawan Rauf (Utrecht University) "The effect of hospital-based antithrombotic stewardship on adherence to anticoagulant therapy"	2017-2018	2.0
6. Supervising of thrombotic nurses		
• Marleen de Graaf-van der Kort (Reinier de Graaf Hospital)	2015-2017	4.0
• Wilma Neeleman-de Zeeuw (Erasmus University Medical Center)	2015-2017	4.0
Total		**62.2**

CURRICULUM VITAE

Albert Dreijer was born on July 24th, 1986 in Leeuwarden and grew up in Franeker, the Netherlands. He studied Pharmacy at the University of Groningen and obtained his Master's degree in 2012. As part of his study, he finished a 6 month research project about the influence of bariatric surgery on the use of medication at the Medical Centre Leeuwarden in Leeuwarden.

In September 2012, Albert started his professional career at the department of Hospital pharmacy of the Reinier de Graaf hospital in Delft. After 1 year he started his residency in hospital pharmacy (supervisors: drs. P.N.J. Langendijk and dr. Jeroen Diepstraten) in the Reinier de Graaf hospital and combined this with a PhD research project at the Erasmus University Medical Centre in Rotterdam, supervised by prof. dr. P.M.L.A. van den Bemt and prof. dr. F.W.G. Leebeek.

In 2019 Albert started working as a hospital pharmacist at the Treant Zorggroep in Emmen, the Netherlands.

Albert is married to Gerdine, and father of Hugo and Filip.