Studies on safety issues in anticoagulant management

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Studies on safety issues in anticoagulant management

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Chapter 1

General introduction

Hemostasis

Blood coagulation is responsible for the prevention of fatal blood loss but also for the occurrence of venous and arterial thrombi in the vascular system, leading to a partial or total interruption of the blood stream. Primary or secondary prevention of venous or arterial thromboembolism (TE) often encompasses the administration of oral and/or parenteral anticoagulant agents. All anticoagulant use increases the risk of bleeding. Bleedings attributable to anticoagulant use can sometimes be fatal. The determination of the ideal type, dosing and timing of anticoagulant therapy is an ongoing challenge for patient care; a delicate balance has to be found between the risk of thromboembolism and bleeding for all individual patients.

The coagulation system is based on well balanced steps regulated by the coagulation proteases, the vessel wall and platelets. The liver is responsible for the production of most of the coagulation proteases like factors V, VII, IX, X, XI, XII, prothrombin and fibrinogen. The coagulation system can be activated in two ways, via the intrinsic and the extrinsic pathway. Thrombin is the central enzyme in blood coagulation, the product of a series of protease directed protein cleavages, starting with the exposure of tissue factor (TF) on the sub-endothelium or at microparticles in the circulation. The tenase and prothrombinase complex jointly further catalyze the transformation of prothrombin into thrombin and result in a burst of thrombin.¹

Different mechanisms lead to the inhibition of coagulation. In one of these mechanisms thrombin in complex with thrombomodulin enables the activation of protein C into activated protein C (APC). APC associated with protein S in turn inactivates activated FV (FVa) and FVIIIa, leading to inhibition of thrombin production via a negative feedback loop.¹

Thrombosis and bleeding

Abnormalities in coagulation can lead to the formation of a thrombus. Arterial TE, a major health problem especially in the elderly population, is associated with conditions such as atrial fibrillation, arteriosclerosis, or the introduction of mechanical aortic/mitral valves prosthesis. Deep venous thrombosis (DVT) and subsequently pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE) is caused by diverse risk conditions including malignant neoplasms, hospital or nursing home confinement, trauma/surgery and neurological disease with extremity paresis. The primary and secondary prevention of potentially life threatening and invalidating TE requires adequate antithrombotic treatment, which consists mainly of

anticoagulant and/or antiplatelet therapy.² The most important adverse effect of anticoagulant treatment is the risk of bleeding. Ideally, when antithrombotic therapy is applied a balance is found between the risk of TE and bleeding.

Anticoagulant agents

In day to day practice a wide range of anticoagulants is available for the prevention of TE.³ In this thesis we discuss safety and efficacy aspects of vitamin K antagonists (VKA) and low molecular weight heparins (LMWH) in different settings. VKA inhibits the activity of the vitamin K dependent procoagulant proteins prothrombin, FVII, FIX and FX, and the anticoagulant proteins C and S. VKA inhibits the process of recycling vitamin K by blocking VKORC1, resulting in a relative vitamin K deficiency in the liver cell. This results in the production of impaired, non γ carboxylated coagulation factors.^{4,5} The anticoagulant effect of LMWH is mainly derived from the anti FXa effect induced by a conformational change of antithrombin (AT). In the presence of LMWH the anticoagulant effect of AT, particularly against FXa, is accelerated.⁵

Anticoagulation assays

Several blood tests are developed to monitor the anticoagulation intensity in patients. The most commonly used test to monitor VKA therapy is the prothrombin time (PT).⁴ This test responds to changes in concentration of F II, VII and X, which are reduced by acenocoumarol and fenprocoumon, VKAs commonly used in the Netherlands. This reduction is proportional to the half-life of the clotting factor; the first days after the (re) initiation of VKA therapy PT mainly reflects the changes in F VII, which has a relatively short half-life of 6 hours. The PT assay is performed by adding calcium and a thromboplastin to citrated plasma and is expressed in seconds. Due to for instance different sensitivity of thromboplastins used the PT initially lacked standardization. In 1982 a calibration model was adapted to standardize reporting by correcting for different thromboplastins used in different laboratories; International Normalized Ratio (INR) = (patient PT/mean normal PT)^{ISI} where International Sensitivity Index (ISI) denotes the thromboplastin used in the local laboratory.⁶ Currently, the intensity of VKA is measured by PT and expressed as INR. Frequent measurement of an individual's INR value is required in order to manage anticoagulation within a therapeutic range (internationally, an INR range of 2.0-3.0 is most common; in this country 2.5-3.5 is the most relevant range).

The anti-Xa assay is designed to monitor the effect of LMWH and unfractionated heparin (UFH). There is no recommendation in guidelines for repeated use of an anti-Xa assay for dose adjustment in patients using LMWH for prophylaxis or treatment options. According to experts in the field, the anticoagulant effect of LMWH only needs to be monitored in obese patients, patients with reduced renal clearance^{7,8} and during pregnancy.⁹ Although there is little firm evidence for appropriate therapeutic anti-Xa ranges (also considering the fact that there is little evidence supporting a strong correlation between anti-Xa activity and efficacy) the therapeutic peak (2-4 hours after subcutaneous injection) window is estimated at 1-2 units/ml for odd LMWH and 0.5-1.0 units/ml for bid dosed LMWH. Renal impairment and multiple therapeutic doses of LMWH can result in bioaccumulation and therefore increased risk of bleeding. Testing anti-Xa level in such patients would seem appropriate.

The thrombin generation (TG) assay offers a global view on hemostasis. This assay can be performed in both platelet poor and platelet rich plasma. TG measures the concentration of thrombin over time formed after triggering coagulation with one of the recommended stimuli: 1pM TF, 1 pM TF + thrombomodulin, and 5 pM TF. TG results in a curve which describes the variation of the amount of thrombin during the activation of coagulation cascade in time.¹⁰ The 2 most important parameters obtained from this curve are peak height, the maximum concentration of thrombin at a certain moment in time and the endogenous thrombin potential which represents the total amount of thrombin produced over time.¹⁰ The position of TG measurement in practice has not been established yet. Eventually, it is likely that simplified versions of TG, for instance based on the whole blood point of care prototype assay¹¹, will allow broad applications, including for predicting TE and bleeding, or to monitor anticoagulant therapy with VKA, LMWH, UFH and NOAC.¹⁰

Thrombosis prophylaxis and CDS

Thrombosis prophylaxis is a major topic, since many hospitalized patients are at increased risk for VTE, due to for instance increased age, immobility, cancer or surgery. The yearly incidence of DVT in the Netherlands is 0.6-1.2 cases per 1000 inhabitants,¹² the reported VTE incidence in hospitalized patients is 100 times greater.¹³ In case of low VTE risk only early ambulation is advised; for patients at increased risk, apart from early ambulation, daily doses of LMWH is the preferred treatment option. Solid evidence of the efficacy of VTE prevention is presented in numerous studies.¹⁴⁻¹⁶ However, large studies show that antithrombotic prophylaxis is underused in the hospital setting, leading to avoidable cases of VTE. In different

studies only as little as 30-50% of the patients received appropriate prophylactic therapy.¹⁷⁻¹⁹ In medical patients the rates of patients receiving appropriate prophylaxis are even lower than in surgical patients.²⁰ Reasons for underutilization include unfamiliarity or disagreement with current guidelines, underestimation of VTE risk or fear for bleeding complications.

Over the last years the use of clinical decision support (CDS) has gained more attention. Prospectively validated risk assessment models (RAM) for VTE risk factors are available for integration in CDS; risk factors for VTE and bleeding are awarded with a score; simply adding the numbers after establishing a cut-off point, results in an advice to whether or not apply prophylactic interventions and in which dose. These prophylactics include pharmacological interventions (LMWH, fondaparinux or UFH) or mechanical interventions (graduated compression stockings, intermittent pneumatic compression). Available RAMs for bleeding risk estimation are not prospectively validated yet.¹⁵ High scores for VTE risk factors and low bleeding scores result in the advice to apply pharmacological interventions, a high VTE risk score combined with a high bleeding score results in the advice to apply mechanical measures and in case of a low VTE and bleeding score only the advice of early ambulation is given. Several studies in different settings have been performed to evaluate the effectiveness of different CDS systems. In most studies a positive effect of CDS was established, translating in increased guideline adherence or even a reduction of the incidence of VTE.^{21,22} In some studies the effectiveness of CDS was temporary. Studies evaluating CDS systems in which a direct link to the ordering system was provided and/or CDS use was mandatory showed the best results.^{21,23,24}

In **chapter 2** of this thesis we present results of a study evaluating a pilot CDS system (from September 1st to December 1st 2013) in the Maastricht University Medical Center+ (MUMC+). CDS was introduced in cooperation with Philips Group Innovation Research, Eindhoven, the Netherlands, on two different wards comprising mainly of medical patients. The ACCP guidelines 2012, the prevention of VTE in nonsurgical patients,¹⁵ were used to build the CDS. The application was installed on 4 stand-alone personal computers in two different wards. The hospital patient data system (SAP, Germany) menu was extended with a dedicated CDS button on the opening page of the patient's record. A direct link to the ordering system of pharmacological or mechanical prophylaxis was not provided. All attending physicians of the wards were trained in the use of the CDS system and motivated to use CDS daily for all admitted patients.

Bridging therapy

Anticoagulation in patients receiving long-term VKA undergoing surgery is challenging in terms of maintaining the delicate balance between bleeding and TE; the patient using anticoagulants is vulnerable for bleeding in the perioperative period. During a preferably short periprocedural period the patient should not be anticoagulated, to avoid bleeding during and after the intervention. The anticoagulation-free interval is minimized by “bridging” with LMWH or UFH which replace the longer acting VKA. The efficacy and safety of bridging with LMWH has however not been unequivocally established.³ In **chapter 3** of this thesis results are presented of a systematic review analyzing the safety and efficacy aspects of bridging therapy. Several studies show that the risk of bleeding during bridging therapy is increased, while TE risk is unknown.²⁵⁻³² Furthermore, guidelines for optimal use of bridging anticoagulation seem poorly adhered to.³³ In **chapter 4** results of a study analyzing guideline adherence in a Dutch University hospital are presented.

In 2012 the American College of Chest Physicians (ACCP) presented their latest guidelines for perioperative management of antithrombotic therapy.³⁴ In the management of perioperative anticoagulation in patients on VKA, 3 options can be considered. First, in procedures with a low bleeding risk and the possibility of local hemostatic measures, such as dental extractions, cataract operations and small dermatologic procedures, it is considered a safe choice to continue VKA use. Second, in patients at low risk of TE, ACCP guidelines recommend stopping warfarin administration 5 days before the intervention and restarting warfarin 12-24 hours after the procedure when adequate hemostasis is secured. Finally, in patients at moderate or high TE risk current ACCP guidelines recommend bridging therapy consisting of parenteral administration of LMWH or UFH in the periprocedural period, combined with interruption of VKA use. The decision to apply bridging anticoagulation should always be based on an assessment of individual patient- and surgery-related factors.³⁴ The suggested TE risk stratification by the ACCP is based mainly on indirect evidence from studies outside of the perioperative setting involving patients with a mechanical heart valve, chronic atrial fibrillation or VTE who either were not receiving anticoagulation or were receiving less-effective treatment.³⁴⁻³⁷ It is conceivable that due to the lack of insight in hypo or hypercoagulability during bridging therapy in individual patients the concept of bridging anticoagulation might be qualified as a ‘black box’. In **chapter 5** we present the results of a study in which the (interactive) effects of the co-administration of VKA and LMWH and surgery on different coagulation assays, including thrombin generation assay, INR, anti Xa assays and the

measurement of concentrations of vitamin K dependent coagulation factors, were assessed.

Venous stenting

Post thrombotic syndrome (PTS) develops in more than 50% of patients with iliofemoral DVT (IFDVT).³⁸ Conventional treatment regimes, comprising of a combination of compression therapy, mobilization and oral anticoagulants, up till now mainly VKA, do not always lead to rapid resolution of symptoms or recanalization of venous occlusions, but are associated with long-term disability. Since several years the use of percutaneous transluminal angioplasty (PTA) and stenting in the venous system in patients with outflow obstructions of the iliofemoral veins has gained more attention. PTA and stenting appears to be effective in terms of improvement of PTS symptoms and has shown to be characterized by good mid- to long-term patency rates in mainly observational studies.³⁹⁻⁴⁵ In acute IFDVT patients in whom catheter directed thrombolysis (CDT) is applied, additional venous stenting immediately following thrombolysis is often deemed indicated in case of underlying venous pathology, such as iliac vein compression syndromes, which may be the cause of the thrombosis in these patients.⁴⁶ Both CDT and stenting procedures are usually followed by anticoagulant therapy with VKA for at least 3 months; patients with PTS usually already use VKA prior to the intervention.

Arterial stenting in combination with antiplatelet therapy has been applied in a larger number of patients for a longer period of time; and as a consequence the body of evidence concerning antithrombotic therapy has grown over time.⁴⁷ However, so far no data evaluating aspects of safety and efficacy for any antithrombotic therapy after *venous* stenting have been published, resulting in the application of a wide range of anticoagulant (VKA and new oral anticoagulants (NOAC)) and antiplatelet therapies) for different periods of time in day-to-day practice. In **chapter 6** of this thesis we present the results of a systematic literature search addressing the issue of antithrombotic therapy after venous stenting. In **chapter 7** the influence of the quality of anticoagulant treatment with VKA after stent placement was evaluated in terms of stent re- occlusion. Time within therapeutic range (TTR) and the proportion of INR values <2.0 were assessed as the main determinants of efficacy in this study. **Chapter 8** provides a summary and general discussion of the contents of this thesis.

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Chapter 2

The effect of clinical decision support on adherence to thrombosis prophylaxis guidelines in medical patients; a single center experience

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Abstract

Introduction

Venous thromboembolism (VTE) is an underestimated health problem. The administration of low molecular weight heparins (LMWH) to the appropriate patients dramatically decreases VTE incidence. Clinical decision support (CDS) might contribute to thrombosis prophylaxis guideline adherence.

Methods

A computerized integrated risk score program was used to estimate VTE and bleeding risk of nonsurgical patients. A VTE risk score of ≥ 4 resulted in an advice to administer LMWH. We selected 64 medical patients before the introduction of CDS (T0) and 64 patients after the introduction (T1). We compared guideline compliance between these groups using χ^2 tests.

Results

No difference between groups was found; Adherence to the guidelines at T0 was 59.4%, the same percentage of 59.4% was found at T1. To evaluate the effect of the introduction of CDS in terms of under and overtreatment we compared the prevalence of over and under treatment at T1 and T0. The OR for receiving under treatment at T1 compared to T0 is 0.48 (95% CI: 0.18-1.30), $p=0.14$. The OR for overtreatment at T1 compared to T0 is 1.66 (95% CI: 0.74-3.73), $p=0.22$.

Conclusion

We found no improvement in guideline adherence towards anti thrombotic prophylaxis in medical patients after the introduction of CDS in this pilot study. There was however a non-significant shift towards over treatment. Possible explanations for these results are the increased awareness of the risk for thromboembolism induced by the study, suboptimal use of CDS and deviation from CDS advice caused by patient's preferences.

Introduction

Deep venous thrombosis (DVT) and pulmonary embolism (PE) collectively referred to as venous thromboembolism (VTE) represent a major health problem for hospitalized patients. The yearly incidence of DVT in The Netherlands is 0.6-1.2 cases per 1000 inhabitants.¹ The reported VTE incidence in hospitalized patients is 100 times greater.² Currently, antithrombotic prophylaxis with low molecular weight heparins (LMWH) or in some cases unfractionated heparin is applied to prevent VTE. The positive effect of antithrombotic prophylaxis in general surgical, orthopedic surgical and nonsurgical patients on the incidence of VTE has been firmly established in different studies.³⁻⁵ However, literature provides evidence supporting the thesis that antithrombotic prophylaxis is underused in the hospital setting, leading to avoidable cases of VTE. Different studies demonstrated that in only 30-50% of the patients indicated for prophylaxis appropriate measures are indeed taken.⁶⁻⁸ The administration of appropriate prophylaxis in medical patients is observed to be even less than in surgical patients.⁹ Initiatives promoting the use of clinical decision support systems (CDS) or simple electronic alerts have gained more and more attention and have proven efficacy in terms of adherence to guidelines and in some cases reduction of VTE incidence.¹⁰⁻¹⁴ Especially in institutions such as university hospitals, with a high throughput of inexperienced medical personnel in combination with a complex patient load, CDS could function as a guide for the management of antithrombotic prophylaxis.

We assessed whether the introduction of a computer based CDS embedded in the hospital patient data system might lead to improved adherence to guidelines for antithrombotic prophylaxis in medical patients.

Methods

CDS

From September 1st to December 1st 2013 a pilot study was performed in the Maastricht University Medical Centre (MUMC+) on the introduction, use and evaluation of a computer based CDS. Institutional review board approval was obtained (METC 13-5-034). Before the introduction of CDS the application of thromboprophylaxis was left to the discretion of the physician, who could consult locally available web based protocols (ODIN), based on international guidelines. By using CDS a protocol based VTE prophylaxis advice is generated, avoiding the need of

consulting the underlying protocol by the prescribing physician. A customized computerized integrated risk score program was used to estimate VTE and bleeding risk of nonsurgical patients, as described below. All physicians involved in the pilot study were collectively informed about the use and function of CDS and were motivated to participate. The first risk assessment for all admitted medical patients was performed within 24 hours after hospitalization and was hereafter repeated daily. The CDS was installed on four stand-alone personal computers on two wards of the Maastricht University Medical Centre (MUMC+). The following inclusion criteria were applied: 1) the patient is non-surgical and admitted to one of the two participating wards and 2) the (expected time) of admission is at least 48 hours. Excluded were 1) patients on therapeutic anticoagulants and 2) patients with active bleeding.

The hospital patient data system (SAP, Germany) menu was extended with a dedicated CDS button on the opening page of the patient's record. The use of this button was not mandatory and if CDS generated a recommendation for antithrombotic prophylaxis, no automatic link to the pharmacotherapeutic ordering system was provided.

The Padua Prediction Score¹¹ for VTE risk factors, endorsed by the ACCP guidelines 2012⁴, was used to compose the CDS data form. This risk assessment model (RAM), prospectively validated in a study with patients not receiving prophylaxis¹⁵ awards each risk factor with a maximum of 3 points. Scores of the different risk factors are computed into a total VTE risk score, by simple addition. VTE risk was considered high at a score of 4 points or more. The bleeding risk was assessed using a non-validated RAM.¹⁶ With a bleeding score of 7 or more points the patient was considered at high risk of bleeding. Both the risk for thrombosis and the risk for bleeding were dichotomized. A VTE risk score of <4 resulted in an advice not to administer prophylaxis, a VTE score of ≥4 led to an advice to administer (weight adjusted) LMWH. A bleeding score of >7 resulted in a warning in CDS that bleeding risk was high, in case the score ≤7 points the announcement 'low bleeding risk' was depicted within CDS.

Assessment of compliance

In the period prior to the introduction of the CDS, when only the MUMC+ protocol, mainly based on ACCP 2008 guidelines, was available for physicians as a guide to prescribe the correct antithrombotic prophylaxis, compliance to antithrombotic guidelines was assessed on two randomly selected dates for baseline measurements (T0). The measurements were repeated on two randomly selected dates towards the end of the CDS pilot period (T1). For an overview of the patient flow and measurements see Figure 2.1. All risk factors for VTE and bleeding included in the

MUMC+ protocol (T0) and the CDS RAMs (T1) were recorded by two independent researchers for all individual patients admitted to one of the participating wards on the day that the sample was taken. The appropriate antithrombotic prophylaxis was established based on the risk stratification methods at hand. In the MUMC+ protocol VTE risk factors are indicated, but no individual weights are awarded and no risk factors for bleeding are stated. In case of perceived increased bleeding risk the advice to administer reduced doses of LMWH, or no LMWH, is given. For the patients assessed at T1 compliance was assessed using the CDS RAMs; for an overview of the risk factors, see Appendix 2.1. For the assessment at T0 all medical records were reviewed, for risk assessment at T1, medical records were reviewed in case the prescribing physician did not use CDS on the sampling day. Pharmacy records were assessed to verify whether the CDS-generated advice on prophylaxis, resulted in the actual administration of the appropriate prophylaxis. Bed rest, generally poorly reported in medical records, was recorded after interviews with nurses of the participating wards on each date of measurement. Guideline adherence was defined as follows: the patient receives the appropriate prophylaxis (pharmacological or no prophylaxis) on the day the sample is taken.

Figure 2.1 Patient flow and measurements

In case guidelines were not followed, the following 2 options were recorded; 1) Under treatment defined as not receiving LMWH, while an indication was present; 2) over treatment defined as receiving LMWH without indication.

Evaluation of CDS use

After termination of the pilot we evaluated the use of CDS; a questionnaire consisting of 4 domains was designed to identify possible barriers for CDS use. The questionnaire is based on perceived barriers impeding guideline adherence among Dutch general practitioners.^{17,18} We identified barriers related to knowledge (e.g. lack of awareness of CDS, lack of familiarity with CDS), barriers related to attitude (e.g. lack of outcome expectancy, lack of motivation), barriers related to behaviour (e.g. patients' preferences not matching recommendations), and environmental factors (e.g. lack of education, lack of time). See Appendix 2.2 for the complete questionnaire. We asked the physicians who worked with CDS to complete the questionnaire anonymously.

Statistical analysis

To detect an improvement in guideline adherence from 50% to 75%, with a power of 80%, 128 (T0: 64, T1: 64) participants were needed. Cumulative first use of CDS of the participating wards is reported. Descriptive statistics were used to determine patient characteristics. Continuous variables are reported as means and their standard deviations (SD); categorical data are presented as counts and percentages. Chi² tests are used to compare categorical variables including the compliance to the antithrombotic prophylaxis guidelines before and after the introduction of CDS. To estimate the strength of the association between the introduction of CDS and observed compliance Phi statistics are used. Student's t-tests were used to compare continuous variables. Under and over treatment was separately assessed. The associations are also expressed as odds ratios (OR) with accompanying confidence intervals (CI). A two sided p-value <0.05 is considered statistically significant. Data were analyzed with SPSS version 22.

Results

The cumulative rate of first use of CDS in days was explored for the full 3 months duration of the pilot. The software that analyzed the cumulative rate of first use was not designed to differentiate between medical and surgical patients; therefore this rate is only an indication for CDS use in medical patients. Results for the 2 different

wards (VEB5 and VAC2) are depicted in Figure 2.2. Ward VEB5 consists of predominantly medical patients; VAC2 is a ward populated by both medical and surgical patients, only medical patients were assessed.

Figure 2.2 Cumulative rate of first CDS use in time (days); ward VEB5 and VAC2

We included 128 patients; 64 patients were included in the baseline measurement (T0), and 64 patients were included in the post CDS introduction measurement (T1). For detailed patient characteristics of included patients at T0 and T1 see Table 2.1. Anticipated bed rest with bathroom privileges for at least 3 days, a major risk factor, was prescribed to 17.2% at T0 and 3.1% at T1. In our two random samples the medical records of in total 96 patients were reviewed (all 64 patients on T0, and 64 minus 32 CDS assessed patients at T1). The CDS score lists were completed on the day the sample was taken in 50.0% of the cases; the remaining patients were evaluated without CDS (17.2%), or on the basis of a CDS advice which was calculated on previous days (32.8%).

According to the local protocol at T0, 45.3% of the patients should have received pharmacological prophylaxis, 6.3% mechanical prophylaxis and 48.4% of patients were not eligible for any thromboprophylaxis. Pharmacological prophylaxis was administered in 50.0% of the cases; mechanical prophylaxis was rarely used, in only 1.6% of the patients.

According to the RAMs for VTE and bleeding risk assessment at T1 21.9% of the patients should have received pharmacological prophylaxis, 6.3% mechanical prophylaxis and 71.9% were not eligible for any antithrombotic prophylaxis. The percentage of patients that received pharmacologic prophylaxis was more than twice as high (45.3%), and mechanical prophylaxis was not used. For an overview of the prescribed antithrombotic treatment modalities see Table 2.2. Adherence to the

guidelines at T0 was 59.4%, the same percentage of 59.4% was found at T1, resulting in a Pearson's χ^2 of 0.00; p-value=1.00.

Table 2.1 Patient characteristics

	T0: 64 patients	T1: 32 of 64 patients ^a	p-value
Age	66.3 (SD: 19.3)	69.2 (SD: 15.1)	0.45
Sex	27 (45.3 %) male	19 (59.4 %) male	0.11
Weight	77.3 kg (SD: 17.6)	67.9 kg (SD: 20.2)	0.02
BMI >30	11 (17.2%)	5 (15.6 %)	0.85
History VTE	2 (3.1%)	5(15.6 %)	0.03
Known thrombophilia	0 (0%)	0 (0%)	0.73
Congestive heart disease and/or COPD	27 (42.2%)	9 (28.1 %)	0.18
Acute infectious and/or rheumatic disorder	35 (54.7%)	13 (40.6 %)	0.19
Active gastro duodenal ulcer	6 (9.4%)	2 (6.3 %)	0.60
Current cancer	9 (14.1%)	6 (18.8 %)	0.55
Hepatic failure and INR >1.5	6 (9.4%)	0 (0 %)	0.15
Platelet count <50 x 10 ⁹ cells/l	2 (3.1%)	0 (0 %)	0.64
eGFR (creatinine clearance) <60 ml/m (<30 ml/l)	23 (2) (35.9% (3.1%))	10 (3) (31.3% (9.4%))	0.65 (0.19)
Bed rest ≥2 days	11 (17.2 %)	1 (3.1%)	0.05
Bleeding <3 months before admission	10 (16.7%)	10 (31.3%)	0.08
Trauma/surgery legs, hips, pelvis <1 month	3 (4.7%)	1 (3.1 %)	0.72

^a At T1 medical records were only reviewed in case the prescribing physician did not use CDS on the sampling day. Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; SD, standard deviation, VTE, venous thromboembolism

Table 2.2 Prescribed antithrombotic treatment

	T0: 64 patients	T1: 64 patients
Pharmacological prophylaxis		
Nadroparin 2,850 IU	21 (32.8%)	20 (31.3%)
Nadroparin 3,800 IU	1 (1.6%)	3 (4.7%)
Nadroparin 5,700IU	5 (7.8%)	3 (4.7%)
Nadroparin 7,600IU	0 (0%)	1 (1.6%)
Tinzaparin 10,000 IU	2 (3.1%)	0 (0.0%)
Tinzaparin 14,000 IU	3 (4.7%)	1 (1.6%)
Tinzaparin 18,000 IU	0 (0%)	1 (1.6%)
Mechanical prophylaxis		
graduated compression stockings (GCS)	1 (1.6%) (received also tinzaparin 14,000 IU)	0 (0.0%) ^a
intermittent pneumatic compression therapy (IPC)	0 (0.0%)	0 (0.0%) ^a

^a At T1 medical records were only reviewed in case the prescribing physician did not use CDS on the sampling day (32 patients); LMWH use was assessed in all cases. Abbreviations: IE, international units

For the 64 patients at T0 protocol was not followed in 26 cases; 13 patients (13/64=20.3%) did not receive antithrombotic prophylaxis while they did have an indication for prophylaxis. The other 13 patients (13/64=20.3%) of this group were treated with antithrombotic prophylaxis without indication. In the 64 patients at T1

also deviation from protocol was found in 26 patients; in this group 7 patients (7/64=10.9%) were undertreated and 19 patients (19/64=29.7%) were over treated; see Table 2.3. To evaluate the effect of the introduction of CDS in terms of under and overtreatment we compared the prevalence of over and under treatment at T1 and T0. The OR for under treatment at T1 compared to T0 is 0.48 (95% CI: 0.18-1.30), $p=0.14$. The OR for receiving overtreatment at T1 compared to T0 is 1.66 (95% CI: 0.74-3.73), $p=0.22$. A summary of the comparison between T0 and T1 in terms of adherence can be found in Table 3. When the clinicians made use of CDS assistance in 12.5% (4/32) of the cases patients did not receive the actual LMWH dose prescribed by CDS.

Table 2.3 Comparison of guideline compliance between T0 and T1

	T0: 64 patients		T 1: 64 patients	
% of the group in need of antithrombotic measure according to MUMC protocol	Pharmacologic: 45.3% (29/64) No prophylaxis: 54.7% (35/64)	% of the group in need of antithrombotic measure according to RAMs	Pharmacologic: 21.9% (14/64) No prophylaxis: 78.1% (50/64)	
% of the group actually received prophylaxis	Pharmacologic: 50% (32/64) No prophylaxis: 50% (32/64)	% of the group actually received prophylaxis	Pharmacologic: 45.3% (29/64) No prophylaxis: 54.7% (35/64)	
% of the group Compliant to protocol	59.4% (38/64)	% of the group compliant to RAMs	59.4% (38/64)	$P=1.00$
% of the group under treated	20.3% (13/64)	% of the group under treated	10.9% (7/64)	OR for under treatment at T 1: 0.48 (95% CI: 0.18-1.30)
% of the group over treated	20.3% (13/64)	% of the group over treated	29,7% (19 /64)	OR for over treatment at T 1: 1.66 (95% CI: 0.74-3.73)

Abbreviations: MUMC, Maastricht University Medical Centre+; RAM, Risk Assessment Model

Finally, we analyzed the outcomes of the questionnaire presented to all CDS users. Five physicians completed this online questionnaire. All participating physicians estimated their knowledge of CDS as sufficient; they were all aware of the fact that CDS was introduced, all had enough software knowledge of CDS use, all received proper instructions and 4/5 physicians rated their knowledge of the patient's risk factors for thrombosis and bleeding as generally sufficient. Barriers related to attitude were perceived: 2/5 participants questioned whether CDS generated the correct VTE

prophylaxis advice for complex patients with several co-morbidities, the average score for experiencing difficulties due to the introduction of CDS (1: 'no problem'-5: 'very difficult') was scored 2.6 (SD: 1.5), 3/5 did not know whether CDS was 'evidence based', 4/5 perceived CDS advices as clear and 4/5 thought that the use of CDS would lead to better patients outcomes. We also inquired after behavioural aspects towards CDS; the question whether patient's preferences influenced the decision to deviate from the CDS advice, was answered with an average 2.4 (SD: 0.5) on a scale from 1 'never' to 5 'very often' and of all participants 2 preferred to use CDS for high-complex patients and 3 preferred to use CDS in both high and low-complex patients. Finally we inquired after environmental factors regarding the CDS use: all participants judged that the use of CDS required a substantial additional time investment and 2/5 had the opinion that a direct link to the ordering system would lead to a decrease in mistakes with regard to LMWH administration.

Discussion

We found no improvement in guideline adherence towards anti thrombotic prophylaxis in medical patients after the introduction of CDS in this pilot study. Guidelines were followed in 59.4% both before and after the introduction of CDS. There was however a non-significant shift towards over treatment, which may be indicative of higher prophylaxis awareness. The finding that CDS did not result in higher guideline adherence is not coherent with results presented in other studies. Several studies demonstrated a positive, often temporary effect on adherence caused merely by the fact that the introduction of CDS was accompanied by increased awareness of the importance of VTE prevention. The introduction of CDS is associated with increased rates of per protocol administration of VTE prophylaxis, increased rates of administration of VTE prophylaxis in general¹⁴ and even with reduced rates of VTE.¹³ The observed lack of improvement in adherence in this pilot study could, at least partially, be caused by the suboptimal use of CDS. Final use of CDS varied between 23.7% and 57.4% for the different wards. A barrier towards implementation of CDS could have been the additional time investment needed as indicated by physicians in the questionnaire; moreover, time consuming separate login procedures were required in order to enter CDS. Doubts whether CDS was based on solid evidence, uncertainty about the correctness of CDS advices for 'complex' patients, experienced difficulties due to the introduction of CDS and deviation from CDS advice caused by patient's preferences as indicated in the questionnaire also might have attributed to the perceived lack of improvement in adherence.

Our study has several weaknesses. In the first place the sample size was small; only 128 patients participated in this pilot study and no follow-up VTE incidences were assessed. Therefore no association with the incidence of VTE could be made. Secondly, VTE risks for patients at T0 were determined using a local protocol that did not include a risk score for bleeding. The RAM used at T1 included a calculated score for bleeding risk. This could have led to a difference in risk perception. The fact that use of CDS required time consuming login procedures and the fact that no link was provided to the ordering system may have been the most important barrier, resulting in the limited impact of CDS in this study.

In contrast to findings in other studies we conclude that introduction of CDS did not have a positive impact on guideline adherence. A non-significant shift towards over treatment was observed following the introduction of CDS. An easily accessible and mandatory CDS linked to the electronic pharmacy system might be needed in order to improve guideline adherence and associated reduction in VTE incidence.

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Appendix 2.1 Example of a completed CDS form

Risk factors VTE

VTE Prevention CDS
VTE CDS	12-11-2013 17:41: 1 dd 0.3 ml Nadroparine (fraxiparine) (2850 IE aXa)
Risico analyse nvt want
Reden
Reden Anders
VTE Risico	Hoog
VTE Risico	Hoog
Actieve kanker (3)	Nee
Eerder doorgemaakte VTE (3)	Nee
Verwacht bedlegerig >2 dgn (3)	Ja
Trombofilie (3)	Nee
Recent trauma/OK (<= 1mnd) (2)	Nee
Leeftijd >= 70 j (1)	Ja
Hart/respiratoir falen (1)	Nee
Hartinfarct/Ischemisch CVA (1)	Nee
Actuele infectie/reuma (1)	Nee
Obesitas (BMI>=30) (1)	Nee
Anticonc/Horm Subst Therapie (1)	Nee
ScoreMax	4
ScoreMin	4
VTE Risico (Door Arts)	Hoog
VTE Risico (Door Arts)	Hoog
Reden
Behandelplan	1 dd 0.3 ml Nadroparine
Behandelplan (Door Arts)	1 dd 0.3 ml Nadroparine
Behandelplan (Door Arts)	1 dd 0.3 ml Nadroparine
Behandelplan Anders
Reden
Opnamegewicht	38,2 kg

Risk factors bleeding

Bloedingsrisico
Bloedingsrisico	Laag
Nierfalen (1-2,5)	Nee
Man (1)	Nee
Leeftijd Categorie (1,5-3,5)	Leeftijd >= 85
Actieve kanker (2)	Nee
Reumatologische aandoening (2)	Nee
Centrale veneuze catheter (2)	Nee
Intensive care (2,5)	Nee
Leverfalen (INR > 1,5) (1)	Nee
Bloedplaatjes < 50 x 10 ⁹ /L (4)	Nee
Bloeding (<= 3mnd opname) (4)	Nee
Actief gastroduodenal ulcus (4,5)	Nee
ScoreMax	3,5
ScoreMin	3,5
Bloedingsrisico (Door Arts)	Laag
Denk aan gebruik plaatjesremmers
Bloedingsrisico (Door Arts)	Laag

Appendix 2.2 Questionnaire for evaluation of CDS (in Dutch)

Kennis

- 1) Was u in de periode dat de pilot CDS VTE prevention actief was (1-9-13/1-12-13) op de hoogte van het bestaan van CDS op uw afdeling?
 - a. Ja
 - b. Nee
- 2) Zo ja, had u voldoende kennis van de software om het programma op de juiste wijze te kunnen gebruiken?
 - a. Ja
 - b. Nee
- 3) Heeft u voldoende instructie over het gebruik van CDS ontvangen?
 - a. Ja
 - b. Nee
- 4) Had u bij gebruik van CDS doorgaans voldoende kennis van de patient om alle risicofactoren (trombose/bloeding) op de juiste wijze in het systeem in te voeren?
 - a. Ja
 - b. Nee

Attitude

- 5) Leidt het gebruik van CDS tot een juist behandeladvies voor complexe patienten met veel comorbiditeit, zoals die veelvuldig op uw afdeling voorkomen?
 - a. Ja
 - b. Nee
- 6) Maakte u voor de introductie van de pilot gebruik van het ODIN protocol om op de juiste wijze tromboprofylaxe voor te schrijven?
 - a. Ja
 - b. Nee
- 7) Was het moeilijk over te stappen naar een nieuwe vorm (CDS) van inschatting van het tromboserisico?
Geef een score van 1-5, waarbij 1= geen enkel probleem en 5=zeer lastig.
1 2 3 4 5 (een score omcirkelen)
- 8) Was CDDS in de gehanteerde vorm (pilot) voldoende 'evidence based'?
 - a. Ja
 - b. Nee
 - c. Weet ik niet
- 9) De door CDS gegenereerde aanbevelingen: (meerdere alternatieven mogen aangekruist)
 - a. Zijn duidelijk
 - b. Wegen alle relevante factoren mee in het behandeladvies
 - c. Zijn 'up to date'
 - d. Zijn makkelijk toepasbaar
- 10) Denkt u dat het gebruik van CDS leidt tot betere patientenuitkomsten m.b.t. DVT-preventie vergeleken met de 'oude' situatie?
 - a. Ja
 - b. Nee

Gedrag

- 11) Speelt de persoonlijke voorkeur van de patient een rol bij het afwijken van volgens protocol voor te schrijven LMWH?
Geef een score van 1-5, waarbij 1= nooit en 5= zeer vaak.
1 2 3 4 5 (een score omcirkelen)

- 12) Hoe vaak heeft u ten tijde van de pilot gebruik gemaakt van CDS bij het bepalen of een patient tromboprofylaxe nodig heeft of niet?
- a. Nooit
 - b. In ongeveer 0-25% van de gevallen
 - c. In ongeveer 25-50% van de gevallen
 - d. In ongeveer 50-75% van de gevallen
 - e. In ongeveer 75-100% van de gevallen
 - f. Altijd
- 13) Ik heb het meest gebruik gemaakt van CDS voor:
- a. Mobiele, laagcomplexen patienten met een op het oog laag DVT risico
 - b. Meer hoogcomplexen patienten
 - c. Zowel de hoog- als laagcomplexen patienten

Omgevingsfactoren

- 14) Hoe beoordeelt u het gebruiksgemak van CDS:
Geef een score van 1-5, waarbij 1=zeer gebruiksvriendelijk, 5=zeer gebruiksonvriendelijk
- 1 2 3 4 5 (een score omcirkelen)
- 15) Open vraag: Op welke wijze zou de gebruiksvriendelijkheid van CDS kunnen worden verbeterd?
Antwoord:.....
.....
.....
- 16) Denkt u dat een directe koppeling tussen CDS en het medicijnbestelsysteem EVS zou leiden tot minder onjuiste voorschrijvingen/onjuiste doseringen van LMWHs.
- a. Ja
 - b. Nee
- 17) Vergt het gebruik van CDS een belangrijke extra tijdsinvestering?
- a. Ja
 - b. Nee
- 18) Heeft CDS in deze vorm een toegevoegde waarde?
Geef een score van 1-5, waarbij 1=zeer zeker, 5=zeer zeker niet
- 1 2 3 4 5 (een score omcirkelen)

Chapter 3

Safety and efficacy of bridging with low molecular weight heparins: a systematic review and partial meta-analysis

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Abstract

Background

Surgical interventions in patients on long term vitamin K antagonist (VKA) treatment create a dilemma; periprocedural interruption of anticoagulation raises the risk of thrombosis, while continuation raises the risk of bleeding. The anticoagulation-free interval is minimized by “bridging” with parenteral anticoagulants. The efficacy and safety of bridging with low molecular weight heparins (LMWH) has however not been unequivocally established.

Methods

We performed an EMBASE and MEDLINE search for studies that compared bridging anticoagulation with continuation or cessation of VKA without bridging; with thromboembolism (TE) and bleeding as outcomes. We identified 878 articles and finally selected 17. Results of individual studies were pooled.

Results

None of the included studies reported significant differences in incidence of TEs between the bridging group and the comparator group; 4 out of 13 studies reported zero TEs. Heparin was identified as a risk factor for bleeding in multivariable adjusted analyses in 3 studies on pacemaker/implantable cardioverter defibrillator (PM/ICD) surgery. In 5 studies (different types of surgery) with unadjusted analyses, bridging was compared to warfarin cessation: 3 studies reported null results for bleeding; 2 studies identified bridging as a risk factor. We pooled a subset of 6 studies regarding postoperative bleeding after PM/ICD surgery and found a relative risk (RR) of 3.03 (95% confidence interval (CI), 1.86-4.95) for bridging compared to continuation of VKA.

Conclusions

While the antithrombotic efficacy of bridging with LMWH has not been demonstrated, increased bleeding risk is observed in different types of surgery. PM/ICD surgery can be safely performed on continued VKA.

Background

Vitamin K antagonists (VKA) still are commonly used agents in the prevention of venous or arterial thromboembolism (TE). Annually, approximately 10% of the patient population on VKA undergoes at least 1 invasive procedure.¹ The treating physician faces a challenge: a delicate balance must be maintained between the risk of TE and the risk of bleeding in the perioperative anticoagulant management. While arterial TE is associated with a high mortality, or in survivors with major disability,² perioperative bleeding contributes to the need for reoperation, transfusion, prolonged hospitalization, and in some cases death.³ In 2012 the American College of Chest Physicians (ACCP) presented the latest guidelines for perioperative management of antithrombotic therapy.^{1,4}

In the management of perioperative anticoagulation 3 options can be considered. First, in procedures with a low bleeding risk and the possibility of local hemostatic measures, such as dental extractions, cataract operations and small dermatologic procedures, it is considered a safe choice to continue VKA use.⁵⁻⁸ Second, in patients at low risk of TE, ACCP guidelines recommend stopping warfarin administration 5 days before the intervention and restarting warfarin 12-24 hours after the procedure when adequate hemostasis is secured. Finally, in patients at moderate or high TE risk current ACCP guidelines recommend bridging therapy consisting of parenteral administration of LMWH or unfractionated heparin (UFH) in the periprocedural period, combined with interruption of VKA use. A problem that occurs when comparing different studies that assess bridging anticoagulation is the fact that there is no standardized definition of “bridging anticoagulation”; studies assess bridging protocols in which different kinds and doses of LMWH, different time points of administration and cessation of VKA and LMWH are advised.^{2,9-17}

The evidence evaluating these 3 options is not very strong,⁴ except for VKA continuation in case of procedures with a low bleeding risk. In general, there is paucity in randomized trials assessing different strategies, and in most cases the evidence is based on single armed cohort studies.^{9,18-21} Furthermore, most available studies have small sample sizes and are therefore underpowered to determine whether a certain management strategy is safe (prevention of bleeding) and efficacious (prevention of TE).^{12,14,16,18,22} Recently, more solid evidence is emerging regarding bleeding risk related to different anticoagulant management options in PM/ICD surgery, indicating that the continuation of VKA might provide a safer option than bridging.^{13,23-26}

We systematically reviewed studies assessing different peri-interventional management options, compared to bridging therapy. Participants in these studies are all chronic VKA users who undergo surgery. We aimed to assess both the safety and

efficacy of the different strategies. Furthermore we performed a meta-analysis comparing studies with bridging therapy to warfarin continuation in PM/ICD surgery; pocket hematoma and non-pocket bleeding risk were assessed. For this review we considered 4 treatment comparisons 1) bridging therapy versus periprocedural cessation of VKA 2) bridging therapy versus periprocedural continuation of VKA, 3) low dose LMWH versus high dose LMWH and 4) early, within 24 hours postoperative restart of LMWH versus late, after 24 hours postoperative restart of LMWH.

Methods

Study selection

We included only studies wherein at least 2 periprocedural anticoagulant regimens were assessed, 1 of which could be classified as bridging anticoagulation, while other regimens consist of periprocedural withdrawal of VKA without administration of heparins, periprocedural continuation of VKA without heparin administration or surgery under sub therapeutic INR without heparin administration. We decided to include studies in which data were assessed of patients with different risk categories for a TE (low, moderate, high) and surgical procedures with different bleeding risks (low, high). The primary outcome is objectively confirmed perioperative TE and is defined as any thromboembolism, death caused by TE, composite score of TE. The secondary outcome is perioperative bleeding and is defined as: minor bleeding, major bleeding, and any bleeding. Major bleeding is defined as any bleeding resulting in death, any intracranial bleeding, and any bleeding that leads to transfusion of packed red cells and/or treatment in a hospital, or joint bleeds. All other bleedings, including pocket hematomas in cardiac device surgery are qualified as minor bleedings. Cohort studies, case control studies, cross sectional studies and controlled trials were eligible. Our study protocol is based on the third edition of the Centre for Reviews and Dissemination guidance for undertaking systematic reviews, York, United Kingdom.

Data sources and searches

We searched MEDLINE (2001-2011, week 24) and EMBASE (2001-2011, week 36) databases. The search strategy can be found in appendix. A further selection was made on title and abstract. The final selection of articles was made after full reading.

Data extraction and quality assessment

Data from individual studies were collected on case report forms consisting of 3 sections: study eligibility, checklist of items for data collection, and quality assessment using the Newcastle-Ottawa Scale (NOS) for cohort studies.²⁷

Data synthesis and analysis

We compared baseline characteristics and type of interventional procedure between continued warfarin therapy and bridging groups on the basis of Fisher's exact test and Student's t-test, in order to assess the comparability of these groups with respect to bleeding risk. In our meta-analysis on PM/ICD surgery the random effects model as proposed by DerSimonian and Laird was chosen; individual studies are weighed according to the method proposed by Mantel-Haenszel and expressed as RRs.²⁸ RRs and 95% confidence intervals of each included study and the overall effect were computed. The primary outcome is total bleeding; bridging therapy is compared to warfarin continuation. We tested for heterogeneity with the Breslow-Day test; we used the method proposed by Higgins *et al*, expressed as I^2 to measure inconsistency of effects of bridging therapy.²⁹ To assess the possibility of bias of the cumulative evidence, publication bias was explored by presenting funnel plots. There were no tests for publication bias carried out, because with the few studies ($n < 10$) included the power of these tests is too low to distinguish chance from real asymmetry.²⁸ We conducted sensitivity analyses in a pre-specified way; the intervention effects were examined according to a) the quality assessment of the individual studies (cutoff point 6 stars) and b) we excluded the randomized trial (1) and the non randomized trial (1) from our analyses. For our analyses we used free access Revman 5.1, provided by the Cochrane collaboration.

Results

Our database search resulted in a total of 878 studies (including duplications), whereof 517 articles were extracted from MEDLINE and 361 from EMBASE. A first selection on title and abstract yielded a total of 35 articles, further restriction after full reading resulted in a set of 17 studies including a subset of 9 regarding PM/ICD surgery. Eight articles were retrieved by hand searching. For a summary of the search see Figure 3.1. All included studies were published in English. For a summary of the included studies see Table 3.1; for a summary of the effect estimates see Table 3.2.

Figure 3.1 Summary of evidence search and selection.

Abbreviations: LMWH, low molecular weight heparins; TE, thromboembolism; VKA, vitamin K antagonists

Table 3.1 Summary of included studies

Study	Design	Sample size	Determinants	Outcome	Population
Ahmed 2010	Retrospective cohort study	459	Bridging, warfarin suspension, warfarin continuation	Pocket hematoma, major bleeding, TE	PM/ICD surgery
Cano 2010	Prospective cohort study	849: 194 on warfarin	5 groups consisting of different antiplatelet and anticoagulant regimens and combinations of these	Pocket hematoma, pocket revision, pericardial effusion, hemothorax, TE	PM/ICD surgery
Chow 2010	Retrospective cohort study	518: 78 on warfarin	Bridging, no bridging	Hematoma, re-operation/surgical evacuation	Pacemaker surgery in elderly
Daniels 2009	Retrospective cohort study	556: 580 procedures	Bridging, warfarin suspension	Minor bleeding, major bleeding, TE	Periprocedural MHV patients
Garcia 2008	Prospective cohort study	1024 (only first procedure)	Bridging, warfarin suspension	Minor bleeding, major bleeding, TE	All patients and AF patients in minor procedures
Ghanbari 2010	Retrospective cohort study	123	Bridging, warfarin suspension, warfarin continuation	Pocket hematoma	PM/ICD surgery
Hammerstingl 2009	Prospective cohort study	703	Protocol based on ACCP guidelines (LMWH versus no LMWH)	Minor bleeding, major bleeding overall bleeding, TE (arterial)	Periprocedural AF patients
Jaffer 2010	Prospective cohort study	492	No, prophylactic dose, full dose post OK LMWH	Minor bleeding, major bleeding, any bleeding, TE	Different types of surgery
Krane 2008	Retrospective cohort study	238: 57 on warfarin, 181 controls	Bridging, warfarin suspension, controls (no vitamin K antagonists)	Estimated blood loss, change of Hgb, packed cells, catheter duration, TE	Robotic assisted radical prostatectomy
Li 2011	Retrospective cohort study	766	Bridging, warfarin suspension, warfarin continuation	Pocket hematoma, systemic bleeding, TE	PM/ICD surgery
Page 2010	Non randomized controlled trial	198	Bridging, warfarin continuation	Minor bleeding, major bleeding, overall bleeding	Catheter ablation.
Rhodes 2009	Retrospective cohort study	77	Bridging, warfarin continuation	Complications, packed cells	Total knee arthroplasty
Robinson 2009	Prospective cohort study	148	4 separate bridging protocols	Hematoma at pacemaker site, TE	PM/ICD surgery

Table 3.1 (continued)

Study	Design	Sample size	Determinants	Outcome	Population
Tischenko 2009	Prospective cohort study	272: 155 on warfarin	Bridging, warfarin continuation, controls (no vitamin K antagonists)	Hematomas, pocket revision, TE	PM/ICD surgery
Tolosana 2009	Randomized controlled trial	101	Bridging, sub therapeutic INR	Pocket hematoma, drainage hematoma, TE	Cardiac device surgery
Tompkins 2010	Retrospective cohort study	1388: 458 on warfarin	Bridging, INR $\geq$ 1.5, INR < 1.5, control group (no vitamin K antagonist use)	Pocket exploration, blood transfusion, hematoma, TE	PM/ICD surgery
Wazni 2007	Cohort study	355	Therapeutic dose enoxaparin, prophylactic dose enoxaparin (bridging), warfarin continuation	Minor bleeding, major bleeding, pericardial effusion, TE	AF ablation

Abbreviations: ACCP, American Congress of Chest Physicians; AF, atrial fibrillation ; Hgb, Hemoglobin ; INR, International Normalized Ratio; LMWH, Low Molecular Weight Heparin; MHV, mechanical heart valves; PM/ICD, pacemaker/implantable cardioverter defibrillator; TE, thromboembolism

Table 3.2 Summary of the effect estimates of the included studies

Study	Comparison	Outcome	Effect estimate (95% CI) or p-value
Ahmed 2010	Bridging-warfarin continuation	Pocket hematoma	p=0.004; significantly more pocket hematomas in bridging group
Cano 2010	5 groups consisting of different antiplatelet and anticoagulant regimens and combinations	Pocket hematoma	OR enoxaparin bridging: 7.10 (95% CI, 3.34-15.09)
Chow 2010	Bridging-warfarin continuation	Pocket hematoma	p<0.001;significantly more pocket hematomas in bridging group
Daniels 2009	Bridging with LMWH, bridging with UFH, warfarin stop	Major bleeding	p=0.26; no significant differences between groups
Garcia 2008	Bridging-warfarin cessation	Clinically significant bleeding	N.R.
Ghanbari 2010	Bridging, warfarin suspension, warfarin continuation	Pocket hematoma	p=0.03; significantly more pocket hematomas in bridging group
Hammerstingl 2009	Protocol based on ACCP guidelines	Bleeding events	p=0.004; total enoxaparin dose significantly increased bleeding risk
Jaffer 2010	No dose, prophylactic dose, full dose post OK LMWH	Bleeding events	OR full dose heparin: 5.1 (95% CI, 2.3-11.6)
Krane 2008	Bridging-warfarin cessation	Risk of transfusion	p=0.04; significantly higher risk of transfusion in bridging group
Li 2011	Bridging, warfarin suspension, warfarin continuation	Bleeding events	p=0.03; significantly more bleedings in bridging group

Table 3.2 (continued)

Study	Comparison	Outcome	Effect estimate (95% CI) or p-value
Page 2010	Bridging-warfarin continuation	Bleeding events	p<0.001; significantly more bleedings in bridging group
Rhodes 2009	Warfarin continuation-bridging	Risk of transfusion	RR: 0.61 (95% CI, 0.20-1.86);
Robinson 2009	4 separate bridging protocols	Pocket hematoma	p<0.001; significantly more pocket hematomas in postoperative LMWH group
Tischenko 2009	Bridging-warfarin continuation-controls	Pocket revision	p=0.46; warfarin continuation compared to bridging
Tolosana 2009	Bridging-warfarin continuation	Pocket hematoma	p=1.00
Tompkins 2010	Bridging-warfarin continuation-controls	Bleeding events	OR for heparin use: 9.88 (95% CI, 3.16-30.91)
Wazni 2007	Therapeutic dose enoxaparin, prophylactic. dose enoxaparin (bridging), warfarin continuation	Major bleeding	p<0.001; significantly more bleedings in therapeutic dose enoxaparin group

Abbreviations: ACCP, American Congress of Chest Physicians; CI, confidence interval; LMWH, Low Molecular Weight Heparin; OR, odds ratio; RR, relative risk; UFH, unfractionated heparin

The main concern about the internal validity of the included observational studies is the fact that the differences between the comparator groups are not corrected for in the majority of the studies, which probably influences the risk estimates of the individual studies substantially.^{11,23,26,30,31} The most important discrepancy between study groups lies in the fact that the ratio of low, intermediate and high TE risk patients differs significantly in the comparator groups, due to the observational design of the studies; patients at high risk of a TE tend to be bridged differently than moderate or low TE risk patients. In Table 3.3 a summary of potential sources of bias in the individual studies is given. NOS scores are reported in the last column. No study was awarded with the maximum of 9 stars. The considerations mentioned above, justify the decision to confine our meta-analysis to studies containing predominantly high TE risk patients undergoing the same procedure, namely PM/ICD surgery.

Table 3.3 Summary of potential sources of bias in individual studies

Study	Selection of non-exposed cohort	Ascertainment of exposure	Comparability cohorts, adjustments for differences	Ascertainment of outcome	Follow up period	Lost to follow up	NOS score
Ahmed 2010	Same community as exposed cohort	Patient records	Lower aspirin use in warfarin continuation group, differences in indications VKA therapy; Fischer's exact test	Record linkage	8 weeks	All subjects accounted for	6
Cano 2010	Same community as exposed cohort	Patient records	No significant differences reported between study groups; multivariable adjusted analyses	Record linkage	7 days	All subjects accounted for	5
Chow 2010	Same community as exposed cohort	Patient records	No differences between study groups reported; multivariable adjusted analyses	Record linkage	6 weeks	12/518 lost to follow up	6
Daniels 2009	Same community as exposed cohort	Patient records, interviews	Bridging group moderate/high TE risk, warfarin cessation group low TE risk participants; univariable analyses	Record linkage	90 days	All subjects accounted for	6
Garcia 2008	Same community as exposed cohort	Patient records	No differences reported between study groups; univariable analyses	Record linkage	30 days	1/1024 lost to follow up	6
Ghanbari 2010	Same community as exposed cohort	Patient records	Warfarin continuation group and bridging group: only high TE risk participants, warfarin cessation group low TE risk; multivariable adjusted analyses	Record linkage	NR	All subjects accounted for	5

Table 3.3 (continued)

Study	Selection of non-exposed cohort	Ascertainment of exposure	Comparability cohorts, adjustments for differences	Ascertainment of outcome	Follow up period	Lost to follow up	NOS score
Hammersti ngl 2009	Same community as exposed cohort	Patient records	No differences reported between groups; univariable analyses, multivariable analyses	Record linkage	30 days	All subjects accounted for	8
Jaffer 2010	Same community as exposed cohort	Patient records	No significant differences reported between study groups; multivariable adjusted analyses	Record linkage	NR	All subjects accounted for	8
Krane 2008	Same community as exposed cohort	Patient records	No significant differences reported between study groups; univariable analyses	Record linkage	NR	3/60 lost to follow up	4
Li 2011	Same community as exposed cohort	Patient records	Study groups differ in age, % high TE risk, indication warfarin; multivariable adjusted analyses, subgroup analyses high TE risk participants	Transtelephoni c evaluation	4 weeks	All subjects accounted for	7
Page 2010	Same community as exposed cohort	Patient records	% Hypertension, serum creatinine level differ between groups; univariable analyses	Medical examination day +1 + telephone questionnaire	4 to 6 weeks	All subjects accounted for	5
Rhodes 2009	Same community as exposed cohort	Patient records	Age, diagnosis for Coumadin differ between groups; multivariable adjusted analyses	Record linkage	90 days	All subjects accounted for	7
Robinson 2009	Same community as exposed cohort; subsequent protocols	Patient records	No significant differences reported between study groups; multivariable adjusted analyses	Record linkage	1-4 weeks	All subjects accounted for	8

Table 3.3 (continued)

Study	Selection of non-exposed cohort	Ascertainment of exposure	Comparability cohorts, adjustments for differences	Ascertainment of outcome	Follow up period	Lost to follow up	NOS score
Tischenko 2009	Same community as exposed cohort	Patient records	No significant differences reported between study groups, only high TE risk participants in warfarin continuation group and bridging group; univariable analyses	Record linkage	1 week	272/447 lost to follow up, no description given	4
Tolosana 2009	Randomized allocation	Patient records	Only high TE risk participants; univariable analyses	Record linkage	45 days	All subjects accounted for	8
Tompkins 2010	Same community as exposed cohort	Patient records	No significant differences reported between study groups; multivariable analyses	Record linkage	5 days	All subjects accounted for	8
Wazni 2007	Same community as exposed cohort	Patient records	No differences reported between study groups; univariable analyses	Medical examination day +1, self reporting	NR	No statement	4

Abbreviations: NOS, Newcastle-Ottawa scale; NR, not reported; TE, thromboembolism; VKA, vitamin K antagonists

Perioperative anticoagulation strategies

In the articles that met our inclusion criteria, we identified 3 strategies used for the management of perioperative anticoagulation: i) bridging anticoagulation in prophylactic or therapeutic doses with LMWH or UFH; ii) the interruption of VKA without bridging therapy; iii) The continuation of VKA with therapeutic or sub therapeutic INR. These 3 comparisons are discussed successively.

Thrombotic events

The primary outcome TE in patients on chronic anticoagulation was assessed in 13 of the 17 included studies. Percentages of the outcome in different studies range from zero (4) to 2.6 (1).^{9,10,12,13,24,32} None of the included studies reported significant

differences in cumulative incidence of TEs with regard to the comparisons made in this review. For the meta-analysis of bridging therapy compared to VKA continuation in PM/ICD surgery; only 3 studies reported on TE and could therefore not be included in these analyses, this number would be too small to yield relevant results.

Bridging therapy and interruption of anticoagulants

Bridging therapy consisting of different LMWH or UFH in both prophylactic and therapeutic doses was compared to cessation of VKA in 8 studies.^{11,23-25,30,32-34} All of these studies had an observational design. In only 2 of these studies authors reported that in patients in whom warfarin was interrupted TE risk was predominantly low and when bridging was applied patients had mainly moderate to high TE risk.^{11,25} This is in accordance with the recommendation by the current ACCP guidelines. The other authors did not specify differences in TE risk. The type of procedures differed between the studies (Table 3.1). All outcomes of interest could be classified as TE, minor bleeding, major bleeding or overall bleeding. The study by Krane *et al.* mentioned an increased risk of transfusion for bridged patients after robotic-assisted radical prostatectomy compared to interrupted VKA patients ($p=0.04$); this analysis was unadjusted.³³ In a retrospective cohort study performed by Daniels *et al.* the comparison of LMWH or UFH to no heparin in patients with mechanical heart valves undergoing different types of surgery resulted in an unadjusted RR of 1.25 (95% CI, 0.73-2.14) for overall bleeding.¹¹ Pooling the results of 7 individual studies for the outcome minor bleeding resulted as expected in heterogeneity ($p<0.001$; $I^2=78\%$).^{11,16,23-25,30,34} Analysis of major bleeding, overall bleeding and TE resulted in heterogeneity as well (results not shown). In 3 studies multivariable adjusted analyses were presented. First, a study performed by Cano *et al.* reported an odds ratio (OR) of 7.10 (95% CI, 3.34-15.09) for pocket hematoma in patients bridged with enoxaparin who underwent the implantation of cardiac rhythm devices compared to no enoxaparin administration.³² Secondly, Tompkins *et al.* reported an OR for heparin use compared to no heparin use of 9.88 (95% CI, 3.16-30.91) for bleeding complications in patients after cardiac device implantation.²³ Thirdly, Li *et al.* computed, after adjusting for age and gender a p-value of 0.02 comparing warfarin cessation to bridging in PM/ICD surgery; the incidence of overall bleeding was higher in the bridging group.²⁴ Ghanbari *et al.* reported in a study on PM/ICD surgery an unadjusted OR of 6.17 (95% CI, 1.6-24) for major device pocket hematoma in a high TE risk group on bridging therapy.²⁵ Finally, Garcia *et al.* and Ahmed *et al.* reported no significant differences in bleeding risk in their studies of patients undergoing minor procedures and PM/ICD surgery, respectively.^{30,34}

Bridging therapy and continuation of warfarin

Bridging therapy consisting of different LMWH and UFH in both prophylactic and therapeutic doses was compared to continuation of VKA in 9 studies^{12-14,23-26,31,34} whereof 6 studies regarding PM/ICD interventions.^{12,13,23-25,34} The 3 remaining studies assessed the comparison in catheter ablation (2) and total knee arthroplasty (TKA) (1). These 9 studies included 7 cohort studies,^{13,14,23-25,31,34} 1 randomized trial¹² and 1 non randomized trial.²⁶ See Table 3.1 for a summary of the included studies. All outcomes of interest could be classified as TE, minor bleeding, major bleeding or overall bleeding. Again, pooling of these studies resulted in unacceptable heterogeneity ($p < 0.001$; $I^2 = 76\%$).

Rhodes *et al.* presented an age adjusted RR of 0.61 (95% CI, 0.20-1.86) for transfusion required, when they compared a group that continued coumadin with a bridging group in TKA surgery.¹⁴ A non randomized trial including patients undergoing a catheter ablation performed by Page *et al.* resulted in overall bleeding in the bridging LMWH group of 78% and 56% in the warfarin group ($p < 0.001$).²⁶ A randomized controlled trial by Tolosana *et al.* resulted in p values of 1.00 for both pocket hematoma and drainage hematoma.¹²

We performed a meta-analysis assessing the risk of minor bleeding (pocket hematoma), major bleeding (pocket revision, drainage hematoma, pericardial tamponade and hemothorax) and overall bleeding in PM/ICD surgery. We included 6 studies with an observational design (5)^{13,23-25,34} and randomized allocation (1),¹² all with unadjusted results. In all studies, except the study performed by Tolosana, the patients on warfarin had a therapeutic INR. The studies performed by Ghanbari, Tischenko and Tolosana included only high TE risk patients. For the outcome minor bleeding we were able to use a subgroup of patients from the study of Li *et al.*, with high TE risk.²⁴ Differences with respect to known risk factors for bleeding (age, male sex, diabetes, concomitant antiplatelet drug use, bleeding disorders, kind and extend of procedure) were assessed between the bridging and continued warfarin group using Fisher's exact test and the Student's t-test.^{9,35,36} Significant differences between these groups are higher proportions of aspirin use in the bridging group in the study performed by Li,²⁴ higher proportions of patients with diabetes in the bridging group in the study by Ahmed *et al.*³⁴ and younger age in the bridging group in studies by Li²⁴ and Tischenko *et al.*¹³ (results not shown).

Homogenous results ($p = 0.29$, $I^2 = 19\%$) were observed regarding pocket hematoma, and a RR of 2.62 (95% CI, 1.41-4.86) was computed. For major bleeding we observed homogenous results too ($p = 0.36$, $I^2 = 8\%$) with a borderline insignificant RR of 3.26 (95% CI, 0.99-10.78). Analyses regarding overall bleeding resulted in a homogenous

result ($p=0.31$, $I^2=16\%$) with a RR of 3.03 (95% CI, 1.86-4.95). In Figure 3.2 the forest plot is presented; Figure 3.3 depicts the funnel plot, wherein the effect sizes of the studies are plotted against the study precision. Excluding the only RCT from our analyses resulted in a homogenous RR of 3.55 (95% CI, 2.88-5.63). The exclusion of methodological poor studies, less than 7 points on the NOS scale, left us with 3 studies and resulted in a homogenous RR of 2.25 (95% CI, 1.12-4.51).

Figure 3.2 Forest plot comparison: bridging versus warfarin continuation outcome: overall bleeding. M-H indicates Mantel-Haenszel, CI confidence interval.

The dose and timing of heparin administration

Of the included studies, 4 assessed the dosage or timing of heparin administration within the context of bridging therapy.^{3,9,10,16} Jaffer *et al.* performed 'propensity score' adjusted analyses in a prospective cohort and observed that patients in different kinds of surgery receiving the full dose of heparin had significantly higher odds of any bleeding and major bleeding than those receiving the prophylactic dose or no bridging: an OR of 5.1 (95% CI, 2.3-11.6) and 4.1 (95% CI, 1.4-12.1) respectively.³ The propensity score is the predicted likelihood that the patient would receive the full dose of heparin.³ Also adjusting for medical and surgical bleeding class did not influence the ORs remarkably. Hammerstingl *et al.* calculated in their prospective cohort study a multivariable adjusted hazard ratio of 1.058 (95% CI, 1.017-1.101) per enoxaparin dosage (mg/kg body weight) for bleeding events.⁹ The possible association between timing of heparin administration and bleeding was assessed by Chow *et al.*, concluding after an unadjusted analysis of a retrospective cohort that the time at which heparin was resumed influenced the incidence of postoperative hematoma

formation in PM surgery (15/21 within 24 hours versus 6/21 after 24 hours: $p<0.001$) [16]. Robinson reported in a multivariable adjusted analysis that any postoperative administered LMWH is a risk factor for wound hematoma ($p<0.001$).¹⁰

Figure 3.3 Funnel plot comparison: bridging versus warfarin continuation outcome: overall bleeding. RR indicates relative risk, SE standard error

Discussion

We systematically reviewed the efficacy and safety of bridging therapy in different procedures. The most important finding of this review is that no conclusion can be drawn regarding the efficacy of bridging therapy; in none of the included studies significant differences were reported in the incidence of TEs between different study groups. Increased bleeding risk is observed in different types of surgery, attributed to bridging anticoagulation. However, effect modification of bridging therapy by the type of surgery is probable; therefore we cannot generalize the latter finding.

We detected heterogeneity between studies due to the fact that different procedures, study designs, and populations were assessed. We therefore were not able to provide pooled risk estimates for most studies, we were only able to report a pooled risk estimate of PM/ICD procedures. In this review recent studies regarding PM/ICD procedures seem somewhat overrepresented, probably due to recently increased attention to the option of continuation of VKA in these low bleeding risk procedures.

In PM/ICD surgery bridging anticoagulation results in a higher bleeding risk compared to perioperative continuation of VKA. This finding is novel. To our knowledge this is the only review in which a pooled RR is presented for the comparison of bridging therapy to continuation of VKA in PM/ICD surgery.

Most of the 17 included studies that assessed bleeding risk produced biased results. In 4 out of 5 high quality studies (a minimum of 8 stars on the NOS scale) bridging was identified as a risk factor for bleeding^{3,9,10,23}; only 1 high quality study reported a null net result.¹² The finding that bridging is a risk factor for perioperative bleeding is supported by 2 reviews regarding low bleeding risk procedures.^{37,38}

The short exposure time to bridging anticoagulation, according to ACCP guidelines 7 to 11 days, might have influenced the detection that no significant differences occurred in incidence of TEs between different study groups; overall TE incidence was low, in some studies zero. Similar findings were reported in other reviews.^{39,40} The net clinical benefit of bridging is therefore unclear. Nevertheless, the risk of a major bleeding can be weighed against the risk of TE, when case-fatality rates are compared. The case-fatality rate for major bleeding is 8-9%. For arterial TE these rates vary from 15% (heart valve thrombosis) to 70 % (stroke), while venous TE carries a 6% rate for death or major disability and a 25% risk for pulmonary embolism.⁴¹ These numbers suggest that one is more likely to accept major bleedings due to periprocedural anticoagulant strategies to prevent arterial TE.⁴¹

A possible explanation for the bleeding risk associated with bridging therapy is provided by Gerotziafas *et al*, who demonstrated that treatment with a combination of VKA and LMWH induces a more profound inhibition of thrombin generation than treatment with VKA alone.⁴² VKA and LMWH administration is usually resumed within 12-78 hours after surgery; LMWH administration is stopped when the INR reaches a value of 2. In this way a period in which the patient might be more vulnerable for a bleeding is established by the early introduction of bridging therapy. Douketis *et al*. demonstrated that bridging anticoagulation with LMWH after interruption of warfarin therapy is associated with a residual anticoagulant effect prior to surgery, which might lead to a higher bleeding tendency.⁴³

In our meta-analysis on PM/ICD surgery bridging is a risk factor for bleeding. However, these analyses should be interpreted with caution, because in none of these, mostly observational studies, adjusted analyses were presented, and only 2 studies scored 8 points or more on the NOS scale. An earlier meta-analysis on a similar topic performed by Jamula *et al*. reported that a strategy of warfarin continuation appears to confer approximately one-half the risk (OR: 0.43; 95% CI, 0.26-0.73) of experiencing an access site bleeding complication compared with a strategy of warfarin cessation or bridging in elective coronary angiography with or without PCI.⁴⁴

The main limitations of this study are the fact that most of the included studies are of poor methodological quality. Furthermore most of our analyses yielded heterogeneous results; hence only 1 pooled risk estimate could be presented.

Based on previous research, as well as on conclusions presented in this article, the question whether the application of fixed dose LMWH bridging therapy, which may lead to increased risk of bleeding in certain patients is always warranted, seems legitimate. Results provided by large randomized trials like the BRIDGE trial, due in 2013, and the BRUISE control trial in PM/ICD surgery will need to shine more light on the safety and efficacy of bridging. Possibly, a more personalized bridging scheme, including not only TE risk and bleeding risk, but also biomarkers including the individual thrombin generating potential may lead to a better safety and efficacy profile of this intervention. On the other hand, the expected large-scale use of new oral anticoagulants like direct thrombin and factor Xa inhibitors with short half-lives raises the question whether there will be a need to bridge patients who use these new agents.

References

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Appendix 3.1 The search strategy for MEDLINE and EMBASE

(bridging OR perioperative prophylaxis OR periprocedural anticoagulant management OR periprocedural anticoagulant treatment) AND (anticoagulants OR antithrombotic agents OR vitamin k OR vitamin k antagonist OR 4-Hydroxycoumarins OR warfarin OR coumadin OR coumatetralyl OR phenprocoumon OR dicoumarol OR tiocloamarol OR brodifacoum OR phenindione OR clorindione OR diphenadione OR lmwh OR low molecular weight heparin OR ardeparin OR certoparin OR enoxaparin OR parnaparin OR tinzaparin OR dalteparin OR reviparin OR nadroparin OR fondaparinux OR UFH OR unfractionated heparin OR heparin) AND (bleeding risk OR bleeding event OR bleeding complication OR thrombotic event OR TE OR stroke OR cerebrovascular incident OR CVA OR venous thromboembolism OR VTE OR pulmonary embolism OR myocardial infarction OR thrombo (wildcard)

Limits Activated MEDLINE: English, German, Dutch, MEDLINE, published in the last 10 years

Limits Activated EMBASE: English, German, Dutch, published in the last 10 years

Chapter 4

Practice of bridging anticoagulation; guideline adherence and risk factors for bleeding

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Abstract

Background

Perioperative bridging with low molecular weight heparins (LMWH) is applied to minimize the risk of thromboembolism (TE). Guidelines characterize patients at risk and strategies to be followed. We assessed guideline adherence of bridging episodes and identified possible risk factors for bleeding in a retrospective cohort study.

Methods

We searched the electronic patient data system of the Maastricht anticoagulation service, the Netherlands. We identified 181 patients on chronic anticoagulation who underwent surgery (222 procedures) and were bridged with LMWH. Guideline adherence was defined in terms of the relation between TE risk and the dose of LMWH administered, the bleeding risk of the procedure and the duration of postprocedural administration of LMWH. Logistic regression was used to identify risk factors for bleeding.

Results

Of all low TE risk patients (n=102) 84.3% was treated with therapeutic doses of LMWH. The median duration of postprocedural LMWH administration was eight days. The 30-day incidence of major bleeding in the entire group (n=222) was 11.3%. Two patients (0.90%) experienced a deep venous thrombosis. Creatinine clearance ≤ 40 ml/min (odds ratio (OR) 5.03, 95% confidence interval (CI) 1.25 to 20.26) and dental procedures (OR 3.32, 95% CI 1.22 to 9.04) were independent predictors for total bleeding.

Conclusion

Guideline adherence was low, leading to prolonged bridging procedures, excess treatment of patients and high bleeding rates. The majority of patients had a low thromboembolic risk profile or underwent low risk procedures. For patients with decreased creatinine clearance reduced doses of LMWH should be considered to reduce bleeding risk.

Introduction

Perioperative interruption of chronic anticoagulation harbours the risk of thromboembolism (TE). To minimize the risk for TE during the anticoagulant free interval, bridging therapy with low molecular weight heparins (LMWH) is applied. This introduces the risk of bleeding. Vitamin K antagonists (VKA) are administered to patients at increased risk of a venous or arterial TE due to for instance venous thromboembolism, atrial fibrillation, mechanical heart valves, or stroke. According to current guidelines LMWH or unfractionated heparin (UFH) in therapeutic dosages is the preferred anticoagulant for high TE risk patients undergoing high bleeding risk surgery. For patients with an intermediate TE risk profile two options are available: therapeutic or prophylactic dosages of LMWH. For patients at low TE risk again two options are available: prophylactic dosages or interruption of VKA without LMWH or UFH. In low bleeding risk procedures VKA should not be interrupted. The perioperative administration of UFH or LMWH as a part of bridging therapy possibly leads to increased bleeding risk associated with sometimes severe consequences like intracranial bleeding with major disability or even death as a result.¹⁻⁴ Although guidelines characterize patients at risk and advise on strategies to be followed, the application of bridging therapy is often guideline discordant. Literature reveals that a wide range of approaches to bridging anticoagulation is in use, possibly due to unfamiliarity with the current guidelines and the weak evidence on which they are based.^{5,6} Evidence from randomized trials is lacking, probably because ethical issues might arise during the design of such a study; available evidence is therefore mainly based on observational studies. The incidence of postoperative total bleeding ranges from 4.1% to 25% in populations subject to diverse bridging regimes undergoing different surgical interventions.^{4,7-9} The incidence of TE ranges from 0% to 2.6% in different studies.^{3,4,10-13} Apart from improvement of adherence to guidelines there is a need of defining patient and procedure related characteristics which might fine-tune the bridging strategy and thereby decrease the incidence of periprocedural bleeding and TE. Until now, renal insufficiency,^{1,14} CHADS₂ (a composite score of congestive heart failure, hypertension, age, diabetes and stroke),^{8,9,13} mitral valve replacement,^{4,15,16} thrombocytopenia,^{8,16} LMWH administration within 24 hours after the procedure,^{16,17} increasing age,^{7,13} and total duration of periprocedural heparin use¹⁸ are the only consistent risk factors for bleeding. Baseline INR in bridging groups is not associated with postoperative bleeding in different studies.^{7,19} It is still unclear if the application of bridging therapy results in decreased TE risk when compared to VKA cessation alone or VKA continuation without the administration of LMWH.²⁰

Our primary goal was to delineate the features of bridging strategies applied in the region around Maastricht, the Netherlands. We intended to assess guideline adherence and to document the incidence of bridging-related bleeding and TE. The secondary goal was to identify possible risk factors for bleeding during bridging therapy, both patient related risk factors and risk factors associated with the bridging strategy itself.

Methods

Cohort

To determine guideline adherence and identify risk factors for major and total bleeding, we retrospectively searched the electronic patient data system of the Maastricht anticoagulation service for the interval of September 2010 until June 2012. This database contains data of approximately 4200 patients in relation to VKA therapy and bleeding complications. Additional medical information for these patients was retrieved from the patient database of the Maastricht University Medical Centre (MUMC+). Institutional review board approval was obtained (METC 11-4-140).

We identified 181 patients (222 procedures) on chronic anticoagulation who received bridging therapy. A broad definition of bridging therapy was used: any period of periprocedural cessation of VKA including the day of the intervention and administration of any dose of periprocedural LMWH or UFH. The following inclusion criteria were determined: 1) participants were bridged as defined above and 2) were on chronic VKA treatment, initiated more than three months ago. Participants, who had 1) additional surgery within 30 days, 2) underwent an emergency procedure, or 3) yielded inconsistent data, (i.e. contradictory information was found in the different databases), were excluded. We sought to report our study according to the recommendations for reporting studies in periprocedural antithrombotic and bridging therapy issued by the ISTH.²¹

Guideline adherence

We determined guideline adherence of bridging episodes; we ascertained the proportion of patients bridged according to the ACCP guidelines for perioperative management of antithrombotic therapy 2008.²² These guidelines are officially adopted and propagated in the MUMC+. For surgical bleeding risk classification we made use of a two tier distribution in our descriptive analyses; Dental procedures, (extraction of 1-3 teeth, implant placement, surgical extraction of wisdom teeth,

surgical root canal treatment, incision of an abscess, and dental hygiene treatment), cataract surgery, small dermatological interventions, and all other procedures with local anticoagulant options were considered low bleeding risk procedures making it possible to continue VKA treatment. All other procedures were qualified as high bleeding risk procedures and therefore warranted bridging anticoagulation according to ACCP guidelines, providing that elevated TE risk was established in the patient. Arterial and venous TE risks were defined as low, intermediate, or high. TE risk in general was defined as a composite score of venous and arterial TE risk. A low, intermediate, or high arterial/venous TE risk was defined as a low, intermediate, or high composite risk respectively; in case of exposure to both an arterial and venous risk the highest score on either risk was expressed as the TE risk. The variable TE risk in general was composed to be able to estimate the combined effect of arterial and venous TE risk on the physician's decision to administer therapeutic doses of LMWH and on bleeding risk in our univariable and multivariable analyses.

Guideline adherence was defined as low TE risk patients receiving prophylactic doses LMWH post procedurally and intermediate to high TE risk patients receiving prophylactic or therapeutic doses post procedurally. Patients without prior surgical bleedings undergoing low risk dental, cataract, or dermatological procedures should not be bridged; continuation of VKA is the preferred option, but for patients who have experienced a prior surgical bleeding bridging is indicated for these low risk procedures. The period of postoperative administration of LMWH should not exceed seven days. We determined the proportion of all patients on long-term acenocoumarol or phenprocoumon therapy, treated within our institution that received postprocedural therapeutic doses of LMWH. In the literature this proportion ranges from 22% to 85% and is associated with major bleeding.⁶

Complications

We documented the incidence of perioperative total bleeding, major bleeding and TE from three days prior until 30 days after the procedure. Major bleeding was defined according to the criteria used by the Federatie van Nederlandse Trombosediensten (FNT) as any bleeding resulting in death, any intracranial bleeding, and any bleeding that leads to transfusion of packed red cells and/or treatment in a hospital or joint bleeds; all other bleedings including hematomas are qualified as minor bleedings. Thromboembolic complications are defined as any objectively confirmed TE, and death caused by TE; myocardial infarction and acute coronary syndrome were excluded due to the difficulty of attributing these events to cardio embolism in the perioperative setting.²¹

Risk factors for bleeding

Primary outcomes were total and major bleeding. Due to the low number of cases we were unable to identify patient characteristics associated with the risk of TE. To assess bleeding risk of the procedure we used in addition to the ACCP risk classification (low, high) the 5 point scale as proposed by Jaffer et al. ranging from minimal bleeding risk (score 1) to critical risk (score 5).⁶ This 5 point scale was used in our univariable and multivariable analyses as an independent variable. Creatinine clearance was divided into three categories: >60, 41-60, and ≤40 ml/min for reasons of an approximate equal distribution of the obtained values among the categories. The postprocedural restart time of LMWH was estimated and rounded to 0.5 days (12 hours). The total duration of LMWH administration was calculated taking into account the intermediate period that the patient did not receive LMWH including the day of the intervention.

Statistical analysis

Descriptive statistics were used to determine patient and procedure characteristics. Continuous variables are reported as means, their standard deviations (SD), and median values; categorical data are presented as counts and percentages. To assess whether the bleeding risk of the intervention (score 1-5), TE risk (low, intermediate, or high), creatinine clearance (ml/min), or age (years) influenced the physician's decision to administer therapeutic dosages of LMWH post procedurally, univariable and multivariable logistic regression were performed with therapeutic dosage of postprocedural LMWH as the outcome.

In order to identify risk factors for total and major bleeding, first univariable and subsequently multivariable logistic regression was applied. For our multivariable models with both total bleeding and major bleeding as outcomes we selected the established risk factors age (years),^{7,13} total duration of periprocedural heparin use (days),¹⁸ and the variables associated in univariable analysis ($p < 0.10$) with total bleeding: dental procedures (yes/no), TE risk (low, intermediate or high), and creatinine clearance (ml/min). In the univariable and multivariable analyses missing values were imputed; we opted for multiple imputations. Besides the original dataset five additional datasets were created using the Chain Monte Carlo Markov method. The results of these six datasets were pooled. To assess the fitting of different models Hosmer-Lemeshow and model chi-square statistic tests were performed. Risks are expressed as odds ratios (OR) and p-values for linear trends are presented. A two sided p -value < 0.05 was considered statistically significant. Data were analyzed with SPSS version 19.0.0

Results

We were unable to classify 12 participants (12 procedures) in any TE risk category; According to the ACCP guidelines these patients were not indicated for VKA use; conditions like thrombophilia without previous venous thromboembolism (VTE) and cardiomyopathy are not mentioned in the risk scheme.

Baseline characteristics

Baseline clinical characteristics are detailed in Table 4.1. The average age was 70.3 years (standard deviation (SD) 11.4) and 59.0% were male. Arterial TE risk was the indication for VKA use in 190 patients (85.6%); low risk atrial fibrillation (AF) with CHADS₂ scores 0-1 was the most prevalent condition in 67/190 patients (35.3%). VTE risk was present in 42 patients (18.9%); the most prevalent condition was VTE more than six months ago: 32/42 (76.2%). 10 patients had both an arterial and venous indication for VKA therapy. Creatinine clearance was decreased (≤ 60 ml/min) in 62/222 (27.9%) of the patients and in 62/126 (49.2%) of the measurements performed. In 96 (43.2%) patients no periprocedural creatinine clearance was determined.

Table 4.1 Baseline and procedure characteristics, anticoagulation and complications

Baseline characteristics		
Men		131 (59.0%)
Age (years)		70.3 $\pm$ 11.4
Arterial TE risk (n=190)	High	42 (27.4%)
	Intermediate	56 (29.5%)
	Low	80 (42.1%)
	Not mentioned in ACCP/CBO guidelines	12 (6.3%)
Venous TE risk (n=42)	High	9 (21.4%)
	Intermediate	1 (2.4%)
	Low	32 (76.2%)
Creatinine clearance (n=222)	>60 ml/min	64 (28.8%)
	41-60 ml/min	42 (18.9%)
	≤ 40 ml/min	20 (9.0%)
	No measurement performed	96 (43.2%)
Procedure characteristics		
Bleeding risk procedures ACCP (n=222)	High	160 (72.1%)
	High bleeding risk procedure	157 (70.7%)
	Bleeding previous surgery	3 (1.4%)
	low	62 (27.9%)
Bleeding risk 5 point scale (n=222)	Low bleeding risk procedure	62 (27.9%)
	Score 1	143 (64.4%)
	Score 2	33 (14.9%)
	Score 3	39 (17.6%)
	Score 4	7 (3.2%)
	Score 5	0 (0.0%)

Table 4.1 (continued)

Anticoagulation characteristics		
VKA (n=222)	Acenocoumarol	200 (90.1%)
	Phenprocoumon	22 (9.9%)
Vitamin K preprocedural (n=6)	Acenocoumarol	0 (0.0%)
	Phenprocoumon	6 (100%)
LMWH postprocedural (n=222)	Prophylactic	23 (10.4%)
	Therapeutic	199 (89.6%)
Stop time VKA (days)	Acenocoumarol	-3.4 ± 1.6 Median: -3.0
	Phenprocoumon	-5.3 ± 3.6 Median: -5.0
Restart time VKA postprocedural (days)	Acenocoumarol	1.4 ± 3.3 Median: 0.0
	Phenprocoumon	2.1 ± 8.0 Median: 0.0
Start time LMWH preprocedural (days)	Acenocoumarol	-3.2 ± 1.7 Median: -3.0
	Phenprocoumon	-6.3 ± 5.1 Median: -4.0
Stop time LMWH preprocedural (days)	Acenocoumarol	-0.9 ± 0.5 Median: -1.0
	Phenprocoumon	-1.3 ± 0.6 Median: -1.0
Restart time LMWH postprocedural (hours)	Acenocoumarol	19.3 ± 9.9 Median: 24.0
	Phenprocoumon	19.3 ± 9.5 Median: 12.0
Stop time LMWH postprocedural (days)	Acenocoumarol	9.6 ± 6.0 Median: 8.0
	Phenprocoumon	13.9 ± 11.9 Median: 10.0
Total duration LMWH (days)	Acenocoumarol	11.2 ± 6.2 Median: 8.5
	Phenprocoumon	17.6 ± 13.8 Median: 13.0
INR day intervention	Acenocoumarol	1.1 ± 0.1
	Phenprocoumon	1.2 ± 0.2
Time INR>2 (days)	Acenocoumarol	8.7 ± 6.9 Median: 7.0
	Phenprocoumon	11.8 ± 10.5 Median: 8.0
Low TE risk and postprocedural LMWH dosage		
Low TE risk (n=102) and prophylactic dose		16 (15.7%)
Low TE risk (n=102) and therapeutic dose		86 (84.3%)
Complications		
Bleeding (n=44)	Transfusion	4 (1.8%)
	Hospital treatment	21 (9.5%)
	Minor	19 (8.6%)

Abbreviations: ACCP, American College of Chest Physicians; AF, atrial fibrillation; CBO, Centraal BegeleidingsOrgaan voor de intercollegiale toetsing; CHADS₂, congestive heart failure, hypertension, age, diabetes and stroke(2); INR, International Normalized Ratio; LMWH, low molecular weight heparin; MHV, mechanical heart valve; TE, thromboembolism; VKA vitamin K antagonist; VTE, venous thromboembolism

Procedure characteristics

Procedure characteristics are detailed in table 1; 222 procedures were performed in 181 patients. In 62 (27.9%) of all cases bridging therapy was applied for a procedure for which bridging was not indicated; all were low risk dental, cataract, or dermatological interventions. A variety of inpatient and outpatient procedures was performed: dental procedures, gastroscopies, and colonoscopies were the most prevalent interventions, see Table 4.2. The majority (143; 64.4%) of all procedures

was classified as minimal bleeding risk procedure according to the Jaffer scale (score 1), no procedures were classified as critical risk (score 5), only seven (3.2%) procedures were assessed as major bleeding risk (score 4). 17 participants underwent two procedures, seven participants underwent three, and two participants underwent four procedures.

Table 4.2 Procedures performed (n=222)

Gastrointestinal	
Endoscopy colon/duodenum with or without biopsy	26
Cholecystectomy	2
Abdominal surgery	7
Haemorrhoids	3
Colon polyp removal	1
Orthopaedic	
Total hip arthroplasty	5
Total knee arthroplasty	4
Intra-articular injections	3
Elbow/foot/shoulder surgery	3
Other	8
Urology	
Prostate biopsy	7
TUR-prostate	4
Bladder cancer surgery	3
Brachytherapy	2
Kidney scope procedure	5
Cystoscopy with or without biopsy	2
Other	7
Dental	
Extractions	37
Implants	10
Dental hygiene treatment	1
Neurosurgical	
Hernia nuclei pulposi surgery	5
Lumbar puncture	1
Vascular	
Varices	2
Angioplasty/stent placement	2
Bypass surgery	1
Plastic	
Hand surgery	6
Dermatologic procedure	8
Entropion surgery	3
Other	3
Interventional radiology	
Heart biopsy	2
Cardiac catheterization	9
Other	2

Table 4.2 (continued)

Other	
ENT surgery	2
Neurolysis	11
Cataract	2
Hernia umbilicalis/inguinalis	4
Breast cancer	4
Breast biopsy	6
Bronchoscopy with or without biopsy	4
Other	5

Abbreviations: ENT, ear, nose and throat; TUR, transurethral resection of the prostate

Anticoagulation

Anticoagulation characteristics are detailed in Table 4.1. The majority of the patients used acenocoumarol as oral anticoagulant: 200 (90.1 %), the remaining 22 (9.9%) used phenprocoumon. The median preoperative stop time of VKA was day -3 (mean -3.4, SD 1.6) and day -5 (mean -5.3, SD 3.6) for acenocoumarol and phenprocoumon, respectively. Vitamin K was used to reverse anticoagulation only in six patients (2.7%); all used phenprocoumon, a VKA with a relative long half-life of 120-200 hours. Acenocoumarol was resumed a median of 0 days (mean 1.4, SD 1.6); phenprocoumon was resumed a median of 0 days (mean 2.1, SD 8.0). LMWH was used as bridging agent of first choice in all patients. The proportion of patients at low TE risk (n=102) treated with therapeutic doses of LMWH post procedurally was 84.3% (n=86). We also explored periprocedural timing of LMWH administration; LMWH therapy was initiated a median 3 days (mean 3.2, SD 1.7) and a median 4 days (mean 6.3, SD 5.1) before and stopped a median of 1 (mean 0.9, SD 0.5 and mean 1.3, SD 0.6) day prior to the planned procedure in acenocoumarol and phenprocoumon users respectively. The median time of postoperative restart of LMWH therapy was 24 hours (mean 19.3, SD 9.9) and 12 hours (mean 19.3, SD 9.5) in acenocoumarol and phenprocoumon users respectively. The median duration of postoperative LMWH administration was 8 days (mean 11.2, SD 6.2) and 13 days (mean: 17.6, SD 13.8) in acenocoumarol and phenprocoumon users respectively. Of all patients undergoing bridging therapy 199 (89.6%) were treated with therapeutic dosages of LMWH after the procedure.

Univariable logistic regression with postprocedural therapeutic dosage of LMWH as the outcome resulted in non significant effects for all variables. No proof was found that the prescribing physician's decision to administer therapeutic dosages of LMWHs was influenced by age, TE risk, surgical bleeding risk, or creatinine clearance. Patients at high TE risk compared to low risk patients had a non significant higher risk of exposure to therapeutic doses (OR 4.22, 95% CI 0.93 to 19.24), p for linear trend=0.06.

Patients with a creatinine clearance within the range of 41-60 ml/min compared to a clearance >60 ml/min had a non significant lower risk of exposure to therapeutic doses (OR 0.43, 95% CI 0.10 to 1.82), p for linear trend=0.88. A high bleeding risk procedure (score 4) on the Jaffer scale compared to a procedure score of 1 resulted in a non significant decreased risk of exposure to therapeutic doses of LMWH (OR 0.24, 95% CI 0.04 to 1.36), p for linear trend=0.11. Multivariable analyses including the aforementioned variables resulted in overall non significant results. Patients at high TE risk compared to low risk had a borderline non significant higher risk of exposure to therapeutic dosages after their intervention (OR 4.96, 95% CI 0.97 to 25.26), p for linear trend=0.05. Patients with a creatinine clearance within the range of 41-60 ml/min compared to clearance >60 ml/min had a non significant lower risk of exposure to therapeutic doses (OR 0.38, 95% CI 0.08 to 1.81), p for trend=0.73. Finally, a bleeding risk score 4 compared to score 1 resulted in a non significant decreased risk (OR 0.27, 95% CI 0.04 to 1.86), p for linear trend=0.23. The goodness of fit of the model was assessed, resulting in a p -value of 0.77 on the Hosmer-Lemeshov test and the model chi-square statistic resulted in a p -value of 0.75.

Complications

The 30-day incidence of total bleeding in the entire group of procedures performed was 44 (19.8%), the incidence of major bleeding 25 (11.3%); there were no deaths, no intracranial bleedings, four patients required a transfusion, and 21 had to be treated in a hospital due to postoperative bleeding. Two patients (0.9%) experienced a deep venous thrombosis and recovered; see Table 4.1.

Risk factors for bleeding

Univariable logistic regression analysis revealed high versus low TE risk (OR 2.59, 95% CI 1.11 to 6.04), p for linear trend=0.03 and dental procedures (OR 2.98, 95% CI 1.45 to 6.13) as risk factors for total bleeding; all other results are non significant. Creatinine clearance ≤ 40 versus >60 ml/min and intermediate versus low TE risk resulted in non-significant elevated risks: OR 2.35, 95% (CI 0.93 to 5.90), p for linear trend=0.07 and OR 1.83, 95% CI 0.77 to 4.33, respectively. To minimize the risk of reversed causality we excluded 18 cases in which VKA were stopped and LMWH administration due to a total bleeding was prolonged; the initial significantly increased risk caused by the total duration of LMWH administration (result not shown) disappeared: (OR 0.94, 95% CI 0.86 to 1.03). After exclusion of the aforementioned 18 cases, dental procedures (OR 3.32, 95% CI 1.22 to 9.04) and creatinine clearance ≤ 40 versus >60 ml/min (OR 5.03, 95% CI 1.25 to 20.26), p for linear trend=0.02 were

identified as independent predictors of total bleeding in a model completed with the variables age, duration of periprocedural use of LMWH, and TE risk. The Hosmer-Lemeshov test resulted in a p-value of 0.47 and the model chi-square statistic yielded a significant result: $p=0.01$.

Finally, we explored major bleeding. Univariable logistic regression revealed intermediate versus low TE risk as a risk factor (OR 3.40, 95% CI 1.17 to 9.93), p for linear trend=0.11. No further risk factors were identified. Our dataset contained only three high TE risk patients due to mitral valve replacements of which one experienced a major bleeding; hospital treatment was necessary (OR 4.06, 95% CI 0.36 to 46.50). In multivariable analysis, using the same model, we again excluded the aforementioned 18 cases to avoid differential misclassification and no significant risk factors were identified. The model as a whole scored a p-value of 0.83 on the Hosmer-Lemeshov test with a p-value of 0.50 on the model chi-square statistic.

Discussion

In our study we found that guideline adherence to bridging therapy in the region around Maastricht, the Netherlands, is not optimal. The most striking finding is that 84.3% of all low TE risk patients was bridged with therapeutic doses LMWH. Low TE risk does not warrant bridging therapy and certainly not with therapeutic doses of LMWH.²² Furthermore we found compared to other studies, high rates of total and major bleedings.^{6,9,23,24} We were unable to find an association of this observed aggressive treatment with anticoagulants and the high bleeding rates, possibly due a lack of contrast in our population. Studies performed by Robinson et al. and Jaffer et al. identified postprocedural therapeutic doses of LMWH as a risk factor for bleeding.^{6,11} In general, bridging therapy exposes the patient to additional risks, also including a risk of heparin-induced thrombocytopenia (HIT).²⁵ Interventions for which no bridging anticoagulation is indicated and VKA administration can simply be continued, represented 27.9% of the total number of procedures performed in our cohort; a fairly high proportion. Possibly due to the fact that the majority of the participants were outpatients, the period of exposure to LMWH was much longer than necessary according to the ACCP guidelines; in outpatients rigidly performed INR testing is often not feasible.²⁶ Furthermore, due to a change in the anticoagulant regime in the outpatient setting the patient's compliance might be at risk; this might introduce an additional risk factor for bleeding or TE. Another possible explanation for prolonged LMWH administration might be the use of too low restart doses of VKA (i.e. the maintenance dose) instead of 1,5 to 2 times higher doses of acenocoumarol and

phenprocoumon as advised in guidelines issued by the FNT.²⁷ Overall TE incidence was low and in concordance with some other studies^{6,9,23,24}; no arterial TE occurred. We conclude that individual clinicians often do not act according to the current bridging guidelines; in the observed cohort the decision to administer therapeutic dosages of LMWH was not or barely influenced by surgical bleeding risk, TE risk, or renal insufficiency. Krahn et al. and Skolarus et al. report similar findings^{5,28}; Gerson et al. on the other hand concluded that most people receiving bridging therapy were managed according to current society guidelines.²⁹ Possible explanations for non adherence are the lack of familiarity with these guidelines, lack of awareness of the significance of consistent bridging practices, disagreement with the guidelines, and resistance to change.³⁰ It is also conceivable that physicians tend to over treat patients because the threat of a TE is considered more severe than the threat of bleeding.⁵

Renal insufficiency appeared an independent predictor for total bleeding. Other studies support this finding^{1,14}; the clearance of LMWH is primarily renal, the plasma half-life increases in patients with renal failure and dose reduction is advised in these patients following the Cockcroft Gault formula.^{8,31} As far as we know only one study performed by Hammerstingl reported high TE risk as a risk factor for perioperative bleeding.⁸ Possibly confounding biased this finding since in our analysis increasing TE risk was only found to be a risk factor for total bleeding in univariable analyses. An unexpected, novel finding is that dental treatment inflicts a very high bleeding risk on patients; most dental treatments do not warrant bridging therapy; instead, VKA continuation in combination with the oral administration of antifibrinolytic agents like tranexaminic acid are advised.²² Several studies report that restarting LMWH in close proximity to the intervention might induce bleeding.^{16,17} Our study does not support these findings; the observed high rate (28.8%) of missing values concerning this variable might have diluted this effect.

Strengths and limitations of study

Our study has some weaknesses; the sample size was small and data were analyzed retrospectively. We were unable to compare different institutions with respect to guideline adherence, so only a local view on bridging practices could be provided. The strengths of our study are: a well defined study population and the observational design that allowed us to establish guideline adherence and identify risk factors for bleeding. We allow comparison of our results with other studies because we reported according to the recommendations for reporting studies in periprocedural anti-thrombotic and bridging therapy, issued by the ISTH.

Conclusions

Guideline adherence to bridging therapy is poor in the observed single regional setting. This results in patients being unnecessarily exposed to LMWH and for too long periods of time. Since bridging is in general associated with increased bleeding risks,^{20,32} it should be avoided in the absence of a good indication. The additional omission of risk stratification based on assessment of renal function further increased bleeding rates. Although these observations are confined to a limited region within one country, there is no reason to expect that this represents a unique and regional problem. Rather, it illustrates the importance of adhering to guidelines for antithrombotic management.

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Chapter 5

Effects of peri-operative bridging with low molecular weight heparins on coagulation during interruption of vitamin K antagonists: a mechanistic study

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Submitted

Abstract

Background

Bridging with vitamin K antagonists (VKA) comprises peri-procedural substitution by low molecular weight heparins (LMWH) upon interruption of VKA. In this exploratory study we investigated the interactive effects of the co-administration of VKA, LMWH and surgery on peri-operative coagulation.

Methods

Blood was sampled daily from day -3 to day +5 in 13 patients. In addition to measurement of INR and anti-Xa activity, thrombin generation (TG) testing and assessment of individual coagulation factors was performed.

Results

At the time of intervention the mean INR was 1.0 (SD 0.1, range 0.9-1.2); the mean anti-Xa at day 0 was 0.19 units/ml (SD 0.20 units/ml, range <0.05–0.60). The intervention caused a 2 to 3 fold increase in TG at day 0. Of all coagulation factors, factor (F) XI had the strongest correlation with TG ($r=0.629$; $p=0.02$) for peak and endogenous thrombin potential (ETP) ($r=0.625$; $p=0.02$). Thrombomodulin-induced reduction of ETP increased from 10.0% (SD 9.2) at day -3 to 18.2% (SD 9.5) at day 0, $p=0.02$. After surgery, FVIII and fibrinogen were significantly increased ($p<0.001$).

Conclusions

In spite of residual anti-Xa activity at the day of the intervention there is a marked increase in TG related to surgery. Peri-operatively, 3 prothrombotic mechanisms were exposed: FXI dependent TG, reduced activity of the activated protein C pathway and postoperative rises in FVIII and fibrinogen. For the complex perioperative management the value of TG or other global assays to monitor the coagulation balance merits further study.

Introduction

Current guidelines advise substitution of longer acting VKA therapy with relatively short acting LMWH in patients at the highest risk of thrombosis in the periprocedural period.^{1,2} Bridging with LMWH therefore is routinely used in patients undergoing invasive procedures that require interruption of VKA, but are deemed too high risk for thromboembolism to allow absence of anticoagulation during the post-intervention period. However, there is only low quality evidence underlying current practice as randomized clinical trials (RCT) were up till recently lacking. The available evidence derived from systematic reviews and meta-analyses suggests that bridging is associated with an increased risk of bleeding. While the bleeding risk may be mostly attributable to the intervention itself, the contribution of fixed, body weight adjusted doses of LMWH in conjunction with stopping/restarting of VKA, may further impair hemostasis in an undesirable manner.³ A recent review showed low rates of thromboembolism in bridged and non-bridged patients of respectively 0.9 and 0.6 percent, but associated high rates of bleeding in bridged patients (13.1% vs. 3.4% all bleeds, and 4.2% vs. 0.9% major bleeds).⁴ Given the observed elevated risk of bleeding associated with this LMWH bridging policy, the routine application of bridging has been recently challenged. In the very recently published BRIDGE study, in patients randomized to placebo, the risk of thromboembolic events was comparably low to the risk in the LMWH bridged subjects (who had a higher risk of bleeding). Based on these outcomes the authors also discussed the issue of thrombogenicity related to the procedure, stating that “The premise that warfarin interruption leads to rebound hypercoagulability and that the milieu of the procedure confers a prothrombotic state, which in turn leads to arterial thromboembolism, is not supported by the results of this trial”.⁵ However, the BRIDGE study included for the large part low risk for thromboembolism patients. Notably, another study showed that there is a 7 times difference in thrombotic risk between more extensive surgery (risks being the highest for hip-surgery or cancer-surgery) compared to less extensive day-surgery risk.⁶ The thromboembolic risks associated with the bridging procedure as well as the underlying mechanisms have not been explored extensively and are therefore largely unknown.

In this explorative study we therefore aimed to investigate the combined effects of cessation of VKA prior to surgery and institution of LMWH in combination with surgery on peri-operative coagulation, assessed by thrombin generation and a panel of its protein determinants.

Methods

Patient selection

During the period from June 2013 until April 2014 13 patients on chronic treatment with VKA for atrial fibrillation (AF), recurrent venous thromboembolism (VTE), or aortic valve replacement who visited the Maastricht Anticoagulation Clinic, the Netherlands, and in whom bridging of anticoagulation was indicated for planned surgery were invited to participate in the study. Institutional review board approval was obtained (METC 12-1-008). All participants gave informed consent; all patients participated once.

Blood samples were collected daily within a time slot of 3 hours and before noon sharp from day -3 to day +5, including the day of the intervention. The following inclusion criteria were applied: 1) At least 3 months acenocoumarol use, a VKA that is commonly used in the Netherlands 2) planned invasive procedure 3) indication for peri-procedural bridging with LMWH 4) mentally competent, and 5) a minimum age of 18 years. Excluded were 1) patients with severe renal failure (MDRD <30 ml/min), 2) patient who were pregnant or breastfeeding and 3) patients undergoing emergency procedures.

Bridging anticoagulation

In all patients acenocoumarol was stopped on day -3, LMWH was installed at day -3 (6 patients) or day-2 (7 patients). The exact bridging regimen was left to the discretion of the prescribing physician, reflecting routine practice. The last dose of LMWH before the intervention was administered at day -1. Acenocoumarol was re-installed at day 0 (1 patient), day +1 (5 patients) or later (7 patients). LMWH was restarted at day 0 (6 patients), day +1 (5 patients), day +2 (1 patient), or day +4 (1 patient).

Blood collection and plasma preparation

Venous blood was collected in 3.2% citrate (w/v) citrated vacutainer glass tubes (Becton Dickinson, Plymouth, UK). Within 1 hour after blood collection platelet-poor plasma (PPP) was prepared using two centrifugation steps: the first at 2000xg for 5 minutes and a second step at 10 000xg for 10 minutes. Plasma aliquots were snap-frozen, stored at -80°C and thawed at 37°C before analysis. The research nurse responsible for the collection of the blood samples recorded the time the sample was taken, the time of LMWH and VKA administration, the type and dose of LMWH and

VKA, and the time of the intervention (day 0) in case report forms (CRF). On day 0 blood was collected before (n=9) or after surgery (n=4).

Thrombin generation measurements

Thrombin generation in platelet-poor plasma was measured using the Calibrated Automated Thrombogram method (Thromboscope BV, Maastricht, The Netherlands), as previously published.[7] The following experimental conditions were used: 0 pM TF with 4 μ M PL at 20:20:60 mol% PS:PE:PC, 1 pM TF with 4 μ M PL in the absence and presence of thrombomodulin (TM) (Thromboscope BV) with a final concentration of 0.65 nM, and 5 pM TF with 4 μ M PL. The threshold of detectable thrombin level with this assay is 10 nM; therefore we imputed for undetectable peak height (PH) values a value of 5 nM, slope=0 and endogenous thrombin potential (ETP)= $0.5 \cdot 5 \cdot (\text{average value of start tail (time)} - \text{lag time (LT)})$ for the concerning reagent).

Measurement of plasma factor levels, INR and anti-Xa

The INR was assessed using Neoplastine-r (STAGO) reagent. Heparin was assessed by means of the anti-Xa levels using the liquid Anti-Xa (STAGO) and a specific LMWH calibrator; the threshold of detectable anti-Xa level with this assay is 0.05 IU/ml. Plasma fibrinogen levels were measured using the Clauss method using liquid Fib as reagent (STAGO). All other coagulation factor levels were determined by one-stage PT-based (FII, FV, FVII, FX) or aPTT-based (FVIII, FIX, FXI, FXII) clotting assays using plasma deficient in factor V, VII, X, XI, or XII, or plasma immune-depleted for factors VIII, or IX, as reagents. AT levels (FX-a inhibitory activity) with Stachrom AT as reagent and protein C levels (Stachrom prot C) were measured using chromogenic assays. All plasma factor level measurements employed commercially available standards (STAGO, Asnières sur Seine, France) calibrated to WHO standards. All assays were performed on a STA-R coagulation analyzer (STAGO).

Statistical analysis

Descriptive statistics were used to determine patient and procedure characteristics. Continuous variables are reported as means, and their standard deviations (SD); categorical data are presented as counts and percentages. When related samples were analyzed Wilcoxon signed-ranks or Friedman tests were applied as appropriate. Non-related samples were tested with Mann-Whitney, Kruskal-Wallis or Student's t-tests as appropriate. Pre and post interventional comparisons were made: day -3 to

day -1 (pre intervention) and day +1 to day +5 (post intervention). To allow linear modeling using linear regression with time expired since LMWH administration as independent variable and anti-Xa levels as dependent variable, anti-Xa values were log transformed ($\ln$ anti-Xa) and measurements in which blood sample collection occurred within 4 hours after LMWH administration were excluded; because LMWH values peak 4 hours after administration.[8] To account for repeated measurements we constructed linear models for all patients individually and calculated the time from LMWH administration to an anti-Xa level of 0.20 IU/ml using these models; the mean values are reported. According to the linear regression model time expired since LMWH administration to reach an anti-Xa level of 0.20 IU/ml is expressed as $(\ln 0.2 - \beta_0 (\text{intercept})) / \beta_1$. Correlations were determined using Pearson's correlation coefficient. Mean values of the different variables for each patient were taken into account. A two sided p-value <0.05 was considered statistically significant. Data were analyzed with SPSS version 22.

Study results are reported according to the recommendations for studies in peri-procedural antithrombotic and bridging therapy issued by the ISTH.⁹

Results

Patient characteristics

Patient characteristics are presented in Table 5.1. The average age of the patients was 64.7 (SD 9.5), 8/13 (61.5%) were male. All participants, 13/13 (100%) were on acenocoumarol treatment for atrial fibrillation (8), DVT (4) and prosthetic aortic valves (1). All patients but one (dalteparin) received therapeutic subcutaneous doses (tinzaparin, nadroparin or enoxaparin) of LMWH peri-operatively: once daily in 12 (92.3%), and twice daily in 1 (7.7%). One of thirteen patients (7.7%) underwent a low bleeding/ thrombotic risk procedure (skin biopsy) the remaining 12/13 (82.3%) underwent a high bleeding/thrombotic risk procedure (umbilical hernia repair (2), ablation for AF (2), orthopedic surgery (4), transurethral resection of the prostate (2), cholecystectomy (1), and nephrectomy (1)).

Table 5.1 Patient characteristics, procedure characteristics, anticoagulation and events

N=13	
Age	64.7 (SD 9.5)
Male	8 (61.5%)
BMI (kg/m ²)	30.7 (SD 5.2)
Anticoagulation	
acenocoumarol	13 (100%)
nadroparin 7,600 IU(2x)	1 (7.7%)
tinzaparin 10,000 IU	2 (15.4%)
tinzaparin 14,000 IU	4 (30.8%)
tinzaparin 18,000 IU	3 (23.1%)
tinzaparin 10,000 IU+ 14,000 IU	1 (7.7%)
enoxaparin 80 mg	1 (7.7%)
dalteparin 2,500 IU	1 (7.7%)
NSAID/Antiplatelet therapy	
COX inhibitors	4 (30.8%)
ADP-receptor antagonists	1 (7.7%)
None	8 (61.5%)
MDRD (ml/min)	
> 60	8 (61.5%)
30-60	5 (38.5%)
< 30	0 (0%)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; IU, international units; MDRD, modification of diet in renal disease; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; TE, thromboembolism;

Changes in plasma factor levels, INR, anti Xa from day -3 to day+5

The mean INR (n=13) at day -3 (the day acenocoumarol was stopped) of 2.6 (SD 0.9, range 1.1–4.8) normalized to a mean of 1.0 (SD 0.1, range 0.9-1.2) at day 0 (the day of the intervention). At day +5 the INR had increased to a mean of 1.8 (SD 0.8, range 1.0-3.0). The mean residual anti-Xa level at the day of the intervention was 0.19 IU/ml (SD 0.20 IU/ml, range 0.05- 0.60) See Figure 5.1 for the course of anti-Xa levels and INR; see Table 5.2 for an overview of per patient anti-Xa levels, dose and timing of LMWH administration at day 0.

Elimination of therapeutic doses tinzaparin after the last pre interventional administration

For all 12 patients who received therapeutic doses of LMWH the time to reach an anti-Xa level of 0.20 IU/ml was calculated. For therapeutic doses of LMWH the models for 12 patients combined, predict a mean duration of 22 hours and 52 minutes (95% CI: 14 h, 40 min-31 h, 20 min); the models for all patients individually ranged from 11 h,

29 min to 45 h, 32 min. An anti-Xa level of ≥ 0.20 IU/ml is considered clinically relevant to prevent thrombosis.¹⁰

Figure 5.1 Mean concentration of plasma factor levels and INR (a) and mean anti-Xa levels (IU/ml) and INR (b) from day -3 to day +5 with their 95% confidence intervals

Abbreviations: INR, International Normalized Ratio; PC, Protein C

The effect of the acute phase on plasma factor VIII and fibrinogen levels

We also examined the peri-operative changes in the concentrations of the acute phase reactants FVIII and fibrinogen. The mean pre interventional FVIII and fibrinogen concentrations were 175.9% (SD 58.9%) and 4.3 g/l (SD 1.1 g/l) respectively; the mean post interventional concentrations were 246.7% (SD 71.4%) and 5.6 g/l (SD 1.7 g/l) respectively; for FVIII, $p=0.002$, for fibrinogen $p=0.003$. The mean concentrations of FVIII and fibrinogen on the day of the intervention for the group of patients in whom blood samples were taken prior to surgery were 165.8% and 4.3 g/l respectively; post-surgery concentrations were 234.0% and 4.5 g/l, $p=0.09$ for FVIII and $p=0.78$ for fibrinogen.

Table 5.2 Overview of per patient anti Xa levels, dose and timing of LMWH administration at day 0, bodyweight, renal clearance and periprocedural bleeding events

Patient	Anti Xa (IU/ml)	Time between last LMWH administration and blood sampling	BMI (kg/m ²)	MDRD (ml/min)	Bleeding (minor/major)
1	< 0.05 IU/ml	31 hours, 45 minutes	36.9	43	No bleeding
2	0.08 IU/ml	22 hours, 15 minutes	28.9	>60	No bleeding
3	0.09 IU/ml	25 hours, 15 minutes	34.4	45	Major
4	0.26 IU/ml	25 hours, 15 minutes	23.7	>60	No bleeding
5	< 0.05 IU/ml	25 hours, 45 minutes	40.7	>60	Minor
6	0.07 IU/ml	26 hours, 45 minutes	23.2	>60	No bleeding
7	0.10 IU/ml	Unknown	30.6	>60	Major
8	0.13 IU/ml	22 hours, 45 minutes	34.2	>60	No bleeding
9	0.13 IU/ml	35 hours, 45 minutes	30.4	39	Major
10	0.14 IU/ml	22 hours, 30 minutes	23.7	34	Major
11	0.26 IU/ml	21 hours, 45 minutes	32.1	>60	No bleeding
12	0.58 IU/ml	14 hours, 0 minutes	30.4	>60	Minor
13	0.60 IU/ml	16 hours, 30 minutes	30.1	42	minor

Abbreviations: IU, international units; LMWH, low molecular weight heparin; MDRD, modification of diet in renal disease

Thrombin generation from day -3 to +5

In Figure 5.2 an overview of ETP and PH triggered with respectively 1pM of TF and 5pM of TF with and without the addition of TM is presented per day and Table 5.3 offers an overview of all TG parameters per day. The mean ETP 1pM TM at day -3 was 292.3 nM * min, then peaked at day 0 to 1003.5 nM * min (in the group of patients in whom blood collection was performed after the intervention), then gradually dropped; day +2 (756.5 nM * min), day +5 (482.3 nM * min). PH 1 pM showed a similar pattern: day -3 54.0 nM, day 0 207.2 nM (in the group of patients in whom blood collection was performed after the intervention), day +2 141.3 nM, day +5 84.6 nM. The mean values of ETP 5 pM and PH 5 pM showed the same pattern.

The correlations between the mean per patient concentration of prothrombin, FV, FVII, FVIII, FIX, FX, FXI, FXII, PC, AT, fibrinogen and different parameters of thrombin generation triggered by all 3 reagents were calculated. Predominantly, weak to moderate, non-significant correlations were observed. Several correlations between FVIII, FXI, and different parameters (all triggers) were all strong and significant ($p < 0.05$); Table 5.4.

Table 5.3 Mean values of ETP (nM · min), PH (nM), LT (min), slope nM/min) and TTP (min) (different triggers) and ETP 1 pM reduction after TM addition (%) from day - 3 to + 5 with their standard deviations and number of measurements per day

Day	ETP 1 pM			ETP 1 pM TM			ETP 1 pM reduction after addition TM			ETP 5 pM		
	Mean	SD	No. observations	Mean	SD	No. observations	Mean reduction (%)	SD	No. observations	Mean	SD	No. observations
-3	292,3	154,1	12	268,9	142,2	12	9,1	334,2	154,0	12		
-2	229,8	232,7	13	179,9	194,7	13	23,5	253,6	263,0	13		
-1	265,4	339,0	13	214,0	278,9	13	19,7	296,1	366,3	13		
0	721,9	393,4	13	608,2	360,9	13	18,7	786,1	367,1	13		
+1	729,5	472,5	13	644,1	437,6	13	14,7	791,1	467,7	13		
+2	756,5	582,4	12	676,0	532,5	12	13,9	802,2	596,7	12		
+3	573,8	519,1	12	527,4	489,7	12	13,0	643,5	510,6	12		
+4	601,6	423,3	13	476,1	413,0	13	24,0	677,0	437,8	13		
+5	482,3	446,9	13	427,0	407,1	13	14,3	514,0	449,5	13		
PH 1 pM*												
-3	54,0	34,4	12	54,4	35,7	12	0,7	73,6	40,8	12		
-2	36,6	44,2	13	35,5	43,8	13	4,7	48,7	60,1	13		
-1	43,6	63,4	13	43,2	62,3	13	0,5	58,7	86,1	13		
0	131,3	87,5	13	130,1	87,4	13	1,4	170,7	99,5	13		
+1	132,6	99,2	13	134,1	97,5	13	-4,2	167,9	118,4	13		
+2	141,3	118,4	12	140,6	118,4	12	0,5	175,3	140,4	12		
+3	110,3	110,8	12	109,8	111,6	12	5,0	139,2	135,1	12		
+4	98,8	91,2	13	95,1	95,1	13	10,3	138,0	114,6	13		
+5	84,6	94,4	13	84,1	94,3	13	1,5	111,2	118,9	13		
LT 1 pM												
-3	9,0	4,6	10	8,9	4,6	10	-	8,5	6,1	11		
-2	7,6	2,6	6	6,7	1,6	5		5,6	1,8	6		
-1	6,0	2,0	5	5,3	1,7	4		7,3	8,0	5		
0	5,2	1,7	11	5,1	1,4	11		4,5	2,9	12		
+1	5,1	1,3	10	5,0	1,0	10		4,7	3,5	11		
+2	4,6	0,6	8	4,6	0,5	8		5,0	4,6	9		
+3	6,1	3,4	8	5,0	0,5	7		6,6	5,5	9		
+4	8,8	4,4	11	7,7	3,3	10		6,1	2,6	11		
+5	8,9	6,5	9	8,7	6,1	9		9,3	7,5	10		
LT 5 pM												

Table 5.3 (continued)

	Mean	SD	No. observations	Mean	SD	No. observations	Mean reduction (%)	Mean	SD	No. observations
			Slope 1 pM			Slope 1 pM TM				Slope 5 pM
-3	17,3	14,7	13	19,0	17,5	13		29,6	21,9	13
-2	10,8	15,7	13	11,1	16,5	13		17,1	24,4	13
-1	12,9	21,5	13	13,5	22,1	13		22,8	39,2	13
0	45,2	36,6	13	48,0	37,7	13		74,4	55,2	13
+1	47,4	40,2	13	50,2	40,9	13		77,7	62,8	13
+2	52,6	49,0	12	55,4	51,7	12		83,1	74,1	12
+3	39,6	44,3	12	42,8	47,8	12		67,5	74,2	12
+4	33,6	35,3	13	34,7	38,8	13		59,6	59,3	13
+5	29,3	38,0	13	30,4	38,7	13		50,4	66,1	13
			TTP 1 pM			TTP 1 pM TM				TTP 5 pM
-3	12,2	5,5	10	11,9	5,7	10		11,2	6,9	11
-2	11,8	4,8	6	9,8	1,8	5		9,4	3,8	6
-1	10,8	5,1	5	8,3	1,8	4		10,5	9,6	5
0	8,7	2,7	11	8,3	2,2	11		7,4	3,7	12
+1	8,3	2,3	10	8,0	1,5	10		7,6	4,8	11
+2	7,5	1,0	8	7,3	0,8	8		8,1	7,1	9
+3	11,1	9,2	8	7,7	0,8	7		10,7	9,4	9
+4	12,5	5,6	11	11,1	4,2	10		9,0	3,5	11
+5	12,4	8,1	9	12,1	7,7	9		12,7	9,7	10

* In TG triggered by 1 pM TF broke down per day - 3 to + 5 PH values below the threshold of 10 nM thrombin ranged from 2/13 patients (15,4%) on day 0 and day + 4 to 8/13 patients (61,5%) of day + 3. Abbreviations: ETP, endogenous thrombin potential; LT, lag time; nM, Nano molar; PH, peak height; pM, Pico molar; SD standard deviation; TM, Thrombomodulin; TTP, time to peak

Figure 5.2 Mean endogenous thrombin potential (a) and peak height (b) from day -3 to day +5 with their 95% confidence intervals

Abbreviations: ETP, endogenous thrombin potential; PH, peak height; pM, Pico molar; TM, Thrombomodulin

To investigate activated PC (APC) resistance, caused by depletion of functional protein C due to VKA use, we compared the decrease in percentage of ETP 1 pM TF caused by the addition of TM for the days with the lowest and highest mean INR; the days in which APC resistance is expected to be minimal and maximal respectively. We computed the mean values of the variable $((\text{ETP 1 pM TF} - \text{ETP 1 pM TF} + \text{TM}) / \text{ETP 1 pM TF}) \times 100$, for all participants on day 0 (day with the lowest mean INR) and day -3 (day with the highest mean INR). The mean values were 9.2 (SD 9.2)% and 18.6 (SD 8.8)% for day -3 and day 0 respectively. The Wilcoxon signed-ranks test resulted in a p-value of 0.002. Additional assessment of correlations between mean per patient clotting factor levels and reduction in ETP 1 pM TF did not yield any significant results (Table 5.4).

Table 5.4 Correlations between mean per patient prothrombin, FV, FVII, FVIII, FIX, FX, FXI, PC, AT, fibrinogen levels, the different parameters of thrombin generation and the reduction of ETP 1pM TF due to TM addition, their significance and the number of observations

	1 pM TF				1 pM TF + TM				5 pM TF				ETP 1pM reduction n by TM			
	Lagtime	ETP	PH	TTP	slope	Lagtime	ETP	PH	TTP	slope	Lagtime	ETP		PH	TTP	slope
FII	-0.169	0.515	0.492	-0.182	0.452	-0.198	0.462	0.487	-0.184	0.458	-0.351	0.543	0.513	-0.368	0.459	0.069
FV	0.046	-0.239	-0.278	0.129	-0.267	-0.083	-0.279	-0.275	-0.059	-0.267	-0.049	-0.238	-0.337	0.025	-0.413	0.509
FVII	0.104	0.367	0.303	0.060	0.242	0.091	0.306	0.297	0.139	0.251	-0.032	0.402	0.341	-0.069	0.288	0.097
FVIII	-0.031	0.493	0.563	-0.197	0.621	0.093	0.523	0.562	0.030	0.607	-0.204	0.458	0.518	-0.329	0.557	-0.327
FIX	0.202	0.456	0.485	0.108	0.502	0.194	0.443	0.481	0.166	0.509	-0.007	0.462	0.469	-0.069	0.489	-0.105
FX	-0.083	0.349	0.385	-0.130	0.381	-0.101	0.331	0.384	-0.092	0.383	-0.257	0.360	0.397	-0.297	0.390	-0.023
FXI	0.303	0.625	0.629	0.199	0.636	0.28	0.597	0.622	0.243	0.633	-0.051	0.623	0.622	-0.112	0.612	-0.110
FXII	-0.260	0.416	0.382	-0.209	0.354	-0.346	0.372	0.384	-0.342	0.363	-0.578	0.418	0.388	-0.538	0.328	0.048
PC	-0.013	0.381	0.358	-0.041	0.330	-0.024	0.328	0.357	-0.003	0.342	-0.215	0.404	0.366	-0.219	0.309	0.137
AT	-0.045	0.086	0.166	-0.138	0.180	0.065	0.112	0.181	0.025	0.202	-0.027	0.075	0.185	-0.059	0.217	-0.328
fib	0.659	-0.186	-0.080	0.536	-0.007	0.649	-0.164	-0.076	0.572	0.007	0.516	-0.182	-0.099	0.471	0.002	0.097

* Correlation is significant at the 0.05 level (2-tailed). Abbreviations: AT, antithrombin; ETP, endogenous thrombin potential; fib, fibrinogen; PC, protein C; PH, peak height; pM, Pico molar; TF, tissue factor; TM, Thrombomodulin; TTP, time to peak

Correlations between INR, anti-Xa, and parameters of thrombin generation

Correlations between mean INR per patient and mean per patient plasma levels of FII, FVII, FIX, FX and protein C were negative, strong, and significant for FII, FVII and protein C. Bonferroni corrected significance of 0.01 was reached for all factors, except the correlations INR-FIX ($r=-0.36$, $p=0.22$) and INR-FX ($r=-0.65$, $p=0.02$) (Table 5.5). Correlations between INR and different parameters of thrombin generation triggered by 1 pM TF with and without the addition of TM, and triggered by 5 pM were moderate and significant ($p<0.05$) for LT (all triggers), and for TTP 1 pM TF+TM and TTP 5 pM TF; weak, inverse correlations were observed between INR and slope, PH and ETP. For comparison we also calculated the correlations between INR and TG on days no LMWH was administered; overall we found similar correlations, p -values <0.05 were reached for LT (all triggers) (Table 5.5).

Table 5.5 Correlations between mean per patient INR, anti-Xa and mean per patient factor levels, different parameters of thrombin generation, their significance and the number of observations

	INR	INR (after at least 1 day no LMWH)	Anti-Xa	Anti-Xa (after at least 3 days no VKA)
FII	-0,777‡	-	-	-
FVII	-0,816‡			
FIX	-0,363			
FX	-0,650*			
PC	-0,781‡			
AT	-			
Lagtime 1pM	0,591*	0,597*	-0,018	0,009
ETP 1pM	-0,424	-0,393	-0,039	0,491
PH 1pM	-0,350	-0,369	-0,697†	-0,793‡
TTP 1pM	0,517	0,423	-0,644*	-0,715†
Slope 1pM	-0,284	-0,370	0,036	0,585*
Lagtime 1pM+TM	0,601*	0,655*	-0,608*	-0,646*
ETP 1pM+TM	-0,369	-0,374	0,023	0,425
PH 1pM+TM	-0,349	-0,372	-0,674*	-0,756‡
TTP 1pM+TM	0,559*	0,506	-0,640*	-0,711†
Slope 1pM+TM	-0,289	-0,386	0,076	0,481
Lagtime 5pM	0,673*	0,662*	-0,602*	-0,642*
ETP 5pM	-0,447	-0,433	0,394	0,697*
PH 5pM	-0,372	-0,337	-0,722†	-0,817‡
TTP 5pM	0,646*	0,534	-0,667*	-0,742†
Slope 5pM	-0,278	-0,351	0,386	0,708†
			-0,630*	-0,640*

* Correlation is significant at the 0.05 level (2-tailed); † Correlation is significant at the 0.01 level (2-tailed);

‡ Correlation is significant at the 0.003 level (2-tailed). Abbreviations: ETP, endogenous thrombin potential; INR, International Normalized Ratio; PH, peak height; pM, Pico molar; TM, Thrombomodulin; TTP, time to peak

Correlations between the mean anti-Xa per patient and different parameters of thrombin generation triggered by all 3 reagents were calculated. A strong correlation between ETP (all triggers) was found, ETP 1 pM TF and ETP 5 pM TF reached a p-value of <0.01 . Other TG parameters showed moderate correlations, a significance level of <0.05 was reached for 9/15 TG parameters. No measurement reached the Bonferroni corrected p-value <0.003 . Overall stronger correlations were observed between the mean per patient anti-Xa and the parameters of TG when only the days that no acenocoumarol was administered for at least 3 days were included in the analysis. The observed correlations for ETP (all triggers) were stronger and Bonferroni corrected p-values <0.003 were recorded for all three ETP triggers. Compared to the correlations that ignored VKA activity higher levels of correlation were also found for LT and PH, slope and ETP (all triggers). A significance level of <0.05 was reached for 12/15 TG parameters (Table 5.5).

Post procedural bleeding and thromboembolism

Our study was explorative in character and not powered to associate outcomes to levels of individual coagulation factors or levels of anticoagulants. No TE (stroke, TIA, systemic embolism) was reported in any patient. However, we observed 4 major bleeding events (30.8%) and 3 minor bleeding events (23.1%) during the 30-day post procedural follow-up; all patients recovered. During the time of the bleeding event all patients had INRs close to 1 (1.0-1.1), but 3 of the patients had residual anti Xa levels of >0.10 IU/ml and 3 patients had impaired kidney function (MDRD 34 ml/min, 39 ml/min, and 45 ml/min respectively). ETP at 1 pM TF 371,4 nM*min (SD 196.7) and PH at 1 pM TF 65,8 nM (SD 41,7) were lower than those of patients without major bleeding; ETP at 1 pM TF 588,5 nM*min (SD 215,0) and PH at 1 pM TF 105,9 nM (SD 50,9), but these differences were not statistically significant ($p=0,11$ and $0,20$ respectively). Similar results were obtained with 5 pM TF activation.

Discussion

Surprisingly, the recently published BRIDGE trial suggests that peri-operative bridging with LMWH would no longer be needed, at least in patients undergoing minor surgical interventions, since the risk of thromboembolism was comparable to the rate observed in non-bridged control patients.⁵ This raises the question whether brief cessation of VKA is associated with any rebound hypercoagulability due to surgery. In order to assess peri-operative coagulation activity in patients undergoing surgical

interventions, we determined the overall impact of cessation of VKA, peri-procedural instillation of LMWH and surgery on net coagulation activity, measured by TG. To understand the nature of any changes in TG, we measured all relevant coagulation proteins that may determine the TG profile.

The results of our exploratory study shows that surgical intervention quickly induced a marked increment in TG peak and ETP values, confirming a “rebound” prothrombotic state. In a further analysis of coagulation proteins we observed that FVIII and FX, but in particular FXI had significant effects on the rate and height of TG. The effect of FXI may support the apparent importance of this protein in driving the risk of postoperative thromboembolism, as illustrated by a recent trial showing better efficacy of FXI inhibition as compared to LMWH.¹¹ Release of tissue factor may engage increased thrombin generation, which through a feedback loop amplifies FXI dependent TG. In this process the contributions of FVIII, FIX and prothrombin are also evident; FVIII was in this setting observed to be a determinant for thrombin generation. Interestingly, the rise in FVIII and fibrinogen occurs gradually, due to the well-known cytokine dependent, acute phase synthesis and the contribution of FVIII to TG may therefore only become evident days after the intervention. Several studies report increased levels of F VIII and fibrinogen until 2 days to 72 hours postoperatively.^{12,13} This may in part explain the protracted risk of thrombosis following surgery. The residual anticoagulant activity may in part be neutralized by the acute phase thrombogenic response following the intervention. Another contributor to the thrombosis risk may be the reduced sensitivity to activated protein C (APC resistance) mimicked in our experiments by adding TM to plasma. While paradoxically, during VKA treatment due to the reduced level of PC, this prothrombotic APC resistance effect is already evident, it does not fully correct when the VKA effect is no longer present as indicated by INR of 1.0 at day 0. The TM reduction is optimized to give a 50% reduction in PH of a normal plasma, but the maximum reduction observed in these patients was around 20%; since PC had at that stage reached normal values, this suggests that other factors contribute to the apparent TM related APC resistance, adding to the risk of thrombosis. Theoretically, the unexplained but steady increase in FV levels may have attributed to this APC resistance effect.

Cessation of VKA and start of LMWH induces marked changes in the coagulation proteome. Strong, inverse correlations between INR and vitamin K dependent pro and anticoagulants were observed. Weak to moderate correlations between INR and TG parameters were recorded; on the other hand, correlations between anti-Xa levels and TG were moderate to strong and significant. The correlations between anti-Xa and TG were stronger after correction for the effect of VKA. In a study in which the

concomitant effect of VKA (in vivo administration) and LMWH (added in vitro) on different parameters of TG was investigated, similar findings were reported.¹⁴ It is possible that the effect on TG of LMWH in combination with AT, which leads to inactivation of FXa and thrombin and subsequent release of TFPI from the endothelium, forming a complex with FXa, TF and FVIIa, is stronger than the effect of the inhibition of prothrombin, FVII, FIX and FX by VKA.

The current study was set up as a mechanistic study, this could be considered as a limitation as it restricts the potential for the assessment of significant risk associations. We did however even within this limited sample observe 4 cases of major bleeding. Three out of 4 had reduced renal function and anti Xa levels >0.1 IU/ml suggesting that bridging with LMWH, especially in patients with renal impairment should be monitored closely. TG tended to be lower in patients who experienced bleeding; no statistically significant difference in levels was observed, most likely due to the limited sample size.

Our study has several strengths. In the first place, as far as we know this is the first study that evaluates bridging therapy by means of a wide range of blood coagulation assays. Results of this exploratory study might offer insight in the so far poorly understood effects of the complex in vivo interaction between VKA and LMWH administration, and the effects of surgery on hemostasis. Secondly, we were able to follow the patients for a 9-day period, so that the whole perioperative bridging period could be evaluated.

We conclude that VKA (acenocoumarol) arrest in bridged patients starting 3 days before surgery gives an effective reduction of INR, but that LMWH may need to be individually tailored. We found that for several patients the ACCP advised timeframe of 24 hours between the last preoperative therapeutic dose administration of LMWH and planned surgery is not long enough to warrant sufficient decline in anti-Xa levels. In spite of residual anti-Xa activity, there was a marked increase in TG related to surgery. Three prothrombotic mechanisms are exposed: FXI dependent TG, reduced activity of the APC pathway and postoperative rise in FVIII and fibrinogen. For the complex perioperative hemostasis management the value of TG or other global assays, to monitor the hemostatic balance, therefore merits further study.

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Chapter 6

Venous stenting after deep venous thrombosis and antithrombotic therapy: a systematic review

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Abstract

Introduction

Over the last years venous stent placement after deep venous thrombosis (DVT) in the iliofemoral veins has gained more attention. The majority of studies evaluating the safety and efficacy of this intervention are of poor methodological quality and the association with antithrombotic therapy has not been studied explicitly. We performed a systematic review to summarize the available literature on antithrombotic management in relation to the safety and efficacy of venous stenting.

Methods

We performed a Medline search to identify studies that addressed anticoagulation and/or antiplatelet treatment options after venous stenting in patients with a prior DVT in the iliofemoral area. We identified 192 articles and finally selected 14 articles for use in this review.

Results

In 86% (12/14) of the included studies anticoagulation was administered to all patients who underwent iliac venous stenting. In 33% of the studies patients received antiplatelet therapy consisting of aspirin and/or clopidogrel (4/12). The duration of antithrombotic treatment was not guided by the stenting procedure in 93% (13/14) of studies. The incidence of re-thrombosis in (sub) groups of only stented patients, ranged from 5% to 25%. Primary, assisted primary, and secondary patency rates 12 months after stent placement ranged from 54%, 72%, 83% respectively to 78%, 83%, 95% in (sub)groups of only stented patients. Rates of major bleedings during long term follow-up ranged from 0% to 11%.

Conclusion

Antithrombotic therapy does not seem to influence any of the outcomes in patients with venous stenting after DVT: recurrent DVT, patency, post-thrombotic syndrome or restenosis and bleeding.

Introduction

For a substantial proportion of patients with deep venous thrombosis (DVT), current treatment strategies are suboptimal. Especially for the group of patients who are at the highest risk for post-thrombotic syndrome (PTS), new treatment modalities are being investigated. Over the last years the use of stenting of the iliofemoral veins has gained more attention. Nowadays, stenting is predominantly used in patients with venous outflow obstructions of the iliac and femoral veins after thrombus removal with catheter directed thrombolysis (CDT) combined with percutaneous mechanical thrombectomy (PMT).¹

Arterial interventions are much better studied than venous interventions and the mechanisms of arterial stent failure are therefore better understood. Iliofemoral venous re-stenosis after stenting probably results from intraluminal fibrosis in post-thrombotic lesions or compression by primary obstructions, while arterial lesions arise from smooth muscle cell proliferation driven by cytokines and growth factors derived from platelets and macrophages.² Platelet adhesion and aggregation likely plays a more important role in high-flow, high shear conditions in the arterial system, coagulation seems more important in the low-flow, low-shear conditions of the venous system.^{2,3} Finally, both in venous injury and atherosclerotic plaque rupture, the exposure of procoagulant tissue factor and other proteins to blood, triggers blood coagulation.³ Therefore the selection of appropriate antithrombotic management is important.

The efficacy and safety profile of venous stenting is evaluated in several clinical studies, but not much attention is given to the optimal duration for the post intervention antithrombotic management.⁴⁻²⁰ In patients receiving venous stents after a DVT, anticoagulation and possibly antiplatelet therapy may play an important role in preventing recurrent thrombosis and subsequent embolization into the vasculature of the lungs. So far, the choice of agent, dosing and duration of anticoagulant and possibly antiplatelet therapy is unclear for patients with venous stents and prior DVT. The lack of methodologically well-designed studies to address this matter is eminent. While conventional anticoagulants such as vitamin K antagonists and low molecular weight heparins have proven to reduce the risk of recurrent DVT dramatically, their role in preventing DVT in patients with venous stents remains unclear. Antiplatelet therapy has proven to be safe and efficacious in patients with arterial stents, but the effect in patients with venous stents, with or without prior DVT also remains unclear. The most recently issued ACCP guidelines (2012) do not advise on extended anticoagulation/antiplatelet therapy after venous stenting; the possibility of stenting after thrombolysis in patients presenting with DVT is not even discussed.²¹ Likewise,

the most recent NICE and ESC guidelines do not discuss venous stenting as a treatment option for patients after a DVT.

Initially we intended to compare the effect of different antithrombotic agents and treatment durations in patients undergoing venous stenting in the iliofemoral area after a first or recurrent DVT, in terms of recurrent DVT, pulmonary embolism (PE), PTS, patency rates and bleeding risk. Since, after our literature search no comparison data were available, we decided to describe and summarize the available literature on different antithrombotic options in relation to these main outcome measures.

Methods

Study selection

Research questions and inclusion criteria of the studies were specified in advance and documented in a protocol. The population of this review consists of patients who underwent venous stenting after venous thrombosis, often in combination with balloon angioplasty preceded by CDT and/or PMT. We only included studies wherein the use of post-interventional antithrombotic therapy was addressed. Antithrombotic therapy consist of: 1) The administration of anticoagulants (vitamin K antagonists, unfractionated heparin (UFH), fondaparinux, low molecular weight heparin (LMWH), direct factor Xa inhibitors, direct thrombin (factor IIa) inhibitors, 2) the administration of antiplatelet drugs: cyclooxygenase (COX) inhibitors: aspirin, ADP-receptor antagonists such as clopidogrel, prasugrel and ticagrelor. We decided to also include studies in which not all participants were stented; a part of the population underwent CDT and/or PMT without stenting. Most studies assessed, with the use of duplex, long-term primary patency rates (i.e. patent stent without re-intervention), assisted primary patency rates (i.e. patent stent after re-intervention without any occlusions) and secondary patency rates (i.e. patent stent after occlusion, with patency ending at the moment the occlusion was present). Other reported outcomes were PTS, recurrent DVT, PE and major bleeding complications. Assessment of PTS was performed with different methods, including the Villalta scale and Venous Clinical Severity scores. No restrictions regarding follow-up period were imposed. In this systematic review case reports, cohort studies, case-control studies, cross-sectional studies and randomized controlled trials were eligible.

Data sources and searches

We searched MEDLINE database up to week 45 of 2013. The search strategy can be found in appendix 6.1. We used MeSH headings for keyword and text word searching and free text for word searching only. No publication date restrictions were imposed; we restricted our search to articles in English. Further selection was made on title and abstract. The final selection of articles was made after full reading.

Data extraction and quality assessment

As far as we know no quality assessment tools designed for specific use in non-comparator, observational studies are available.²² For the quality assessment of individual studies we made use of the Newcastle-Ottawa Scale (NOS); this tool is designed for cohort studies.²³ We selected 5 relevant items and prioritized them in our quality assessment (see appendix 6.2). Each item can be awarded with a star, resulting in a maximum of 5 stars. The following items were assessed: representativeness of the cohort, ascertainment of the exposure, assessment of the outcome, length and adequacy of the follow-up. Data collected from individual studies were reported on case report forms consisting of 3 sections: study eligibility (i.e. type of intervention and outcome), checklist of items for data collection (i.e. characteristics of the participants and study design), and quality assessment using the adapted NOS scale for cohort studies.²³ Data extraction was performed by one reviewer (PE), supervised by the second reviewer (AtC).

Data analysis

Patency rates in most of the included studies were estimated using the method as proposed by Kaplan-Meier. Differences between groups were assessed using the Student's *t*-test; other outcomes were presented as means with their standard deviation or as percentages. Due to the lack of comparator studies in our review no meta-analysis could be performed.

Results

Inclusion and quality assessment

Our MEDLINE database search resulted in a total of 192 studies. For a summary of the search see Figure 6.1. A first selection on title and abstract yielded a total of 27 articles, further restriction after full reading resulted in a set of 14 studies. We identified 12 cohort studies (6 prospective,^{4-7,9,10} 4 retrospective studies,^{8,11,14,17}

2 studies with an unclear character),^{13,18} 1 trial¹⁵ and 1 case report.¹² In only 1 cohort study a comparison with another treatment modality was made; stenting was compared to anticoagulation alone.⁴ We included 3 studies in which the full population was stented;^{8,13,17} one additional study allowed full subgroup analysis of the patients that underwent stenting.¹¹ In 10 studies between 15%¹⁵ and 89%¹¹ of the population was stented. In all included studies the patients underwent CDT and/or PMT and/or angioplasty and stenting and were prescribed to anticoagulation and/or antiplatelet agents and/or graded compression stockings. For a summary of the included studies see Table 6.1.

Figure 6.1 Summary of evidence search and selection

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; PTS, post thrombotic syndrome

Table 6.1 Summary of the included studies

Study	Design	Inclusion criteria	Sample size	Intervention	Outcome
1.AbuRahma 2001	Prospective cohort study	Iliofemoral DVT	51 patients; (group 1: 33 anticoagulation alone, group 2: 18 endovascular interventions (10 patients stented))	Anticoagulation versus anticoagulation+ CDT; balloon venoplasty+stenting	Recurrent DVT; PE; patency rates; survival; bleeding, CEAP, mortality
2.Dayal 2005	Prospective cohort study	Acute/chronic critical thrombotic occlusions at different sites	25 patients; 15 patients stented	CDT; PMT; balloon venoplasty+stenting; antithrombotic therapy	Recurrent DVT; patency rates; survival; bleeding
3a.Sillesen 2005	Retrospective cohort study	Iliofemoral DVT; onset <2 weeks; open popliteal veins	45 patients; 30 patients stented	CDT; balloon venoplasty+ stenting; antithrombotic therapy	Recurrent DVT; reflux; patency rates
3b.Bækgaard 2009	Prospective cohort study	First acute IFVT; <14 days since diagnosis; age<60; open popliteal vein	101 patients(103 limbs); 57 limbs stented	CDT; balloon venoplasty+stenting; antithrombotic therapy	Complications (including PTS); venous reflux; patency rates
4.Husmann 2007	Retrospective cohort study	First DVT; symptoms <1 week	11 patients; all stented	Thrombolysis; thrombectomy; stenting; antithrombotic therapy	Complications; patency rates; valve function
5.Köbel 2007	Prospective cohort study	Acute extensive ilioacaval DVT; symptoms<3 weeks	37 patients; 36 limbs stented	CDT; balloon venoplasty+stenting; antithrombotic therapy	Patency rates; clinical outcomes
6.Raju 2009	Cohort study	Confirmed DVT	159 patients; all stented	Percutaneous recanalization; balloon venoplasty+stenting; antithrombotic therapy	Patency rates; CEAP; QOL; VAS; swelling; recurrent DVT; PE; mortality
7.Grommes 2011	Prospective cohort study	Confirmed DVT; life expectancy >6 months	12 patients; 3 patients stented	CDT; balloon venoplasty+stenting; antithrombotic therapy	Recurrent DVT; PE; patency rates; bleeding
8.Oguzkurt 2010	Case series	Confirmed DVT; Phlegmea cerulea dolens	7 patients; 3 patients stented	Manual aspiration thrombectomy; CDT; balloon venoplasty+stenting; antithrombotic therapy	Recurrent DVT; symptoms (for all participants)
9.Titus 2010	Retrospective cohort study	Confirmed DVT	38 patients; 40 limbs stented	Angioplasty+ stenting; antithrombotic therapy	Recurrent DVT; bleeding; PE; patency rates; CEAP
10.Wahlgren 2010	Cohort study	Chronic PTS	50 patients; 20 patients endovascular surgery	Guide wire recanalization; stenting; antithrombotic therapy	Patency rates; venous clinical severity score; recurrent DVT; PE; mortality
11.Manninen 2011	Prospective cohort study	Acute DVT; symptoms <2 weeks	56 patients; 9 patients stented	CDT; balloon venoplasty+stenting; antithrombotic therapy	Patency; iliofemoral and crural veins; PTS; recurrent DVT; PE; mortality
12.Sharifi 2012	Trial (RCT)	Confirmed DVT; Severe symptoms; femoral popliteal veins or more proximal veins affected	183 patients; 2 groups (92 anticoagulation alone, 91 endovascular interventions (27 patients stented))	Anticoagulation versus Percutaneous thrombectomy; local low dose thrombolytic therapy; balloon venoplasty+stenting; anticoagulation	Recurrent DVT; PE; PTS; bleeding; duration hospitalization; leg edema; skin induration; subjective change; mortality
13.Nayak 2012	Retrospective cohort study	PTS; age>18 years; available follow-up records	44 patients; 39patients, (45 limbs stented)	Endovenous laser ablation; balloon venoplasty+stenting; antithrombotic therapy	CEAP (pre-post); overall improvement; symptoms: pain, swelling, ulcer

Abbreviations: CDT, catheter-directed thrombolysis; CEAP, clinical, etiology, anatomy, pathophysiology; DVT, deep venous thrombosis; IFVT, iliofemoral venous thrombosis; PE, pulmonary embolism; PMT, percutaneous mechanical thrombectomy; PTS, post-thrombotic syndrome; QOL, quality of life; VAS, visual analogue scale.

One study was excluded from quality assessment; a case report.¹² Two studies were awarded with the maximum score of 5 stars.^{9,15} The mean follow-up of the different studies ranged from 7 months⁷ to 5 years.⁴ There were 3 studies with a complete follow-up: 1 retrospective⁸ and 2 small prospective studies;^{6,9} 3 studies did not provide any statement on lost of follow up.^{5,7,13} In Table 6.2 a summary of potential sources of bias in the individual studies is presented. NOS scores are reported in the last column. All the included studies reported data on anticoagulant therapy, antiplatelet therapy or the use of compression stockings.

General study characteristics

In 86% of the studies only patients with prior DVT (12/14 studies) were included; 2 studies included patients with occlusions due to DVT or external compression.^{6,17} In 57% of the studies (8/14) only patients with acute DVT were included;^{4,5,8-10,12,14,15} both participants after an acute or chronic DVT were assessed in 36% of the studies (5/14);^{6,7,11,13,17} in 1 study only patients with chronic DVT were assessed.¹⁸ The age in the different study populations ranged from a median 29 [5] to a mean age of 58¹². Graded compression stockings at 30-40 mm Hg for at least 6 months were prescribed in 36% of studies (5/14). Risk factors for DVT were presented in several studies; the prevalence of thrombophilia (e.g. factor V Leiden mutation, antithrombin III deficiency, protein C deficiency, antiphospholipid antibodies) ranged from 17% to 68% and the prevalence of cancer ranged from 4%¹⁸ to 22%.⁴

Studies

Abu Rahma et al. in 2001, compared anticoagulation alone (n=31) to CDT plus venoplasty/stenting (n=18) in patients after acute iliofemoral DVT;⁴ 56% (10/18) of the latter group was stented. Three patients (17%) in the intervention group had thrombophilia and 9/31 (29%) in the comparator group; all patients with thrombophilia as well as all stented patients were on indefinite anticoagulant therapy. All other patients received warfarin for 6 months and in case of pulmonary embolism for 9-12 months.

Dayal et al. included 25 patients with acute and chronic critical thrombosis or occlusions at different anatomical sites in their study published in 2005.⁶ Participants underwent PMT, CDT, and lesions resistant to CDT were stented. Fifteen out of 25 patients (60%) received stents. Lifelong anticoagulation was prescribed to 24/25 patients. Data on thrombophilia were not presented.

Table 6.2 Quality assessment of the individual studies

Study	Representativeness of the cohort	Ascertainment of exposure	Ascertainment of outcome	Follow-up period	Lost to follow-up	NOS score
1. AbuRahma 2001	Somewhat representative	Surgical records	Record linkage	63 (group 1), 51 (group 2) months (mean)	19/55, no description of the lost	4
2. Dayal 2005	Somewhat representative	Surgical records	Record linkage	11 months (mean)	Complete follow-up	4
3a. Sillesen 2005	Somewhat representative	Surgical records	Record linkage	24 months (median)	Follow-up rate unclear, no description of the lost	4
3b. Bækgaard 2009	additional selection criteria	Surgical records	Record linkage	50 months (mean)	No statement	3
4. Husmann 2007	Somewhat representative	Surgical records	Record linkage	22 months (mean)	Complete follow-up	4
5. K ölbel 2007	Somewhat representative	Surgical records	Record linkage	27 months (median)	Complete follow-up	5
6. Raju 2009	truly representative	Surgical records	Record linkage	48 months (maximum)	No statement	4
7. Grommes 2011	Somewhat representative	Surgical records	Record linkage	7 months (mean)	No statement	3
8. Titus 2010	Venous occlusive disease (not all prior DVT)	Surgical records	Record linkage	10.5 months (mean)	7/36, description provided of the lost	4
9. Wahlgren 2010	additional selection criteria	Surgical records	Record linkage	23 months (mean)	16/19, no description of the lost	3
10. Manninen 2011	Somewhat representative	Surgical records	Record linkage	42 months (median)	9/56, no description of the lost	4
11. Sharifi 2012	Somewhat representative	Surgical records	Record linkage	30 months (mean)	14/183, description provided of those lost	5
12. Nayak 2012	additional selection criteria	Surgical records	Record linkage	11.7 months (mean)	21/44, no description of the lost	2

Abbreviations: DVT, deep venous thrombosis

Sillesen et al. presented in 2005 their results of a retrospective analysis of outcomes of CDT in 45 patients with acute iliofemoral DVT.¹⁴ Treatment modalities consisted of CDT and, in case of the presence of residual thrombus, angioplasty plus stenting; thirty of 45 patients (67%) were stented. Thrombophilia was diagnosed in 30/45 (67%) of patients. All patients received warfarin for at least 12 months.

Bækgaard et al. 2009 reported on the same but extended population (101 patients, 103 limbs) as Sillesen et al, besides the earlier 45 patients 56 extra patients were included in three extra years of inclusion, all patients were followed prospectively. All patients underwent CDT and 57/103 (55%) of limbs were stented.⁵ Anticoagulation treatment was given for at least 12 months to all participants; 54% of the population was diagnosed with thrombophilia.

In 2007 Husmann et al. published a retrospective analysis of 11 stented patients with acute DVT and May-Thurner disease.⁸ No data on thrombophilia were presented. Warfarin was installed for 6 months for all participants.

Kölbel et al. presented in 2007 results on 37 patients (44 limbs) with acute, extensive DVT of the ilio caval segment.⁹ Patients underwent CDT and in 36/44 limbs (82%) stents for underlying stenosis or residual thrombosis were placed. Twenty-five out of 32 patients tested (78%) for thrombophilia were tested positive for 1 or more hypercoagulable disorders. In patients with bilateral thrombosis this percentage was even higher 6/7 (86%). Warfarin therapy for 6 months was prescribed to all participants.

Raju et al, 2009.¹³ included during 9 years 167 limbs of 159 unselected patients with total occlusions of the iliac vein (acute and chronic DVT); all were stented. Of all patients, 44/159 (34%) were diagnosed with 'significant thrombophilia' prior to the intervention. Long-term aspirin use was prescribed early in the study; patients with a known thrombophilia received additional warfarin. This practice was changed over time; Fondaparinux was used for 4-6 weeks in all and long-term anticoagulation was installed for selected patients (recanalizations ≥ 3 segments, suprarenal stents, thrombophilia).

Grommes et al, 2011 studied a population of 12 patients (13 procedures), 11 patients with chronic or acute DVT in the lower extremities and 1 patient with superior caval vein thrombosis.⁷ All patients underwent CDT and 3/12 (25%) were stented. Patients received anticoagulant therapy as advised in the ACCP guidelines 2008: 3 months for provoked DVT and 6 months for idiopathic DVT.

Oguzkurt et al. presented in 2009 a small case series of 7 patients with phlegmasia cerulea dolens secondary to acute iliofemoral DVT of which 3 had underlying May-Thurner disease.¹² CDT and stent placement procedures in 3/7 (43%) were used as

adjunctive procedures to endovascular treatment with manual thrombectomy. All patients received warfarin for 6 months.

In 2010 Titus et al. retrospectively reviewed the charts of a population consisting of 36 patients (40 limbs) with acute or chronic iliofemoral DVT or occlusions caused by external compression.¹⁷ Underlying thrombophilia was diagnosed in 22% of the patients checked. All patients underwent angioplasty and were stented; thrombolysis was performed in 52.8% of the cases. All patients received anticoagulation for 6 months (warfarin at INR 2-3 or Lovenox).

Wahlgren et al, 2010 conducted a study with a population of 50 patients (51 limbs) diagnosed with chronic PTS; 21 limbs (38%) underwent endovascular and/or surgical treatment.¹⁸ All procedures consisted of angioplasty plus stenting. Thrombophilia testing of the total population resulted in 15/50 (30%) positive results; in the stented population this was 10/20 (50%). Stented participants received oral anticoagulation for at least 6 months and aspirin for 1 month additionally.

Manninen et al. conducted in 2011 a study involving 56 patients with acute DVT extending to high femoral or iliac vein.¹⁰ All patients were treated with CDT; nine out of 56 (16%) received 1 or more stents. Participants received warfarin for 6 months. Thrombophilia was established in 34% of the patients.

Sharifi et al. performed a randomized trial in 2012 comparing conservative anticoagulation therapy to percutaneous endovenous interventions plus anticoagulation (PEVI). The patient population of 183 patients consisted of patients with symptomatic proximal DVT.¹⁵ In the PEVI group 27/90 (30%) of the patients were stented. All patients in the PEVI group received aspirin for a minimum of 6 months in addition to warfarin.

In 2012 Nayak et al. performed a study with a population of 44 patients (39 stented, 45 limbs) with PTS and acute or chronic DVT. Endovascular interventions were performed to treat established PTS and one or more stents were placed. In the subgroup of stented patients significant improvements after stent insertion were reported regarding the variables any pain and any swelling. Aspirin 81 mg /day was administered to all participants; warfarin was only given when patients were already using warfarin prior to the intervention; no compression stockings were prescribed after the procedure.¹¹

Antithrombotic therapy

Oral and/or parenteral anticoagulation was administered to all patients who underwent iliac venous stenting in 86% of the included studies (12/14)^{4-10,12,14,15,17,18} only in two studies (2/14) anticoagulation was not installed in all participants.^{11,13} In

the study performed by Nayak, only patients who were on warfarin prior to stent insertion received post-intervention anticoagulation; all participants, including those on warfarin received aspirin at daily doses of 81 mg.¹¹ In the study performed by Raju, only patients with thrombophilia received warfarin. A not specified proportion of the population received only aspirin to maintain long-term stent patency.¹³ This practice was changed over time (not specified); later fondaparinux for 4 to 6 weeks was prescribed for all patients and long-term warfarin for selected patients (recanalizations ≥ 3 segments, suprarenal stents, thrombophilia); no reason was provided for this change of practice and no differentiation was made between these regimes in terms of outcomes.¹³ Anticoagulant management in the included studies therefore can roughly be divided in 3 regimes: 1) Warfarin administration with a target International Normalized Ratio (INR) of 2-3 for 3 to 6 months concurrent with LMWH in the initial phase or in case of renal insufficiency UFH administration until the INR reaches a value of 2 for 2 consecutive days: 58% of studies (8/12), 2) Warfarin with an target INR of 2-3 for at least 12 months concurrent with LMWH or UFH in the initial phase: 17% of studies (2/12) and 3) warfarin administration, INR range 2-3 indefinitely concurrent with initial LMWH or UFH: 17% of studies (1/12). One remaining study could not be classified in one of these categories (8%). These regimes were supplemented in 33% (4/12) of studies with 4) antiplatelet administration; aspirin or aspirin plus clopidogrel. For a detailed summary of antithrombotic therapy in the different studies see Table 6.3.

Outcomes

Recurrent DVT and occlusions

The incidence of recurrent DVT was reported in 12/14 studies;^{4,5,7-10,12-15,17,18} The incidence of re-thrombosis in (sub) groups of only stented patients ranged in different studies from 5%¹⁵ to 25% (early re-thrombosis 6%; late re- thrombosis 19%).¹³ In the study by AbuRahma et al. recurrent DVT occurred in 3/18 (17%) of the patients in the endovenous intervention group and in 2/8 (25%) in the comparator group.⁴ A fairly low rate of DVT was reported by Titus; 1/36 (3%),¹⁷ Sillesen;¹⁴ 1/45 (2%) and also in the study by Kölbel 1/44 limbs (2%).⁹ Bækgaard et al. reported 6/103 (6%) recurrent DVT (3 early within days and 3 late within 2-3 years).⁵ Four patients (31%) experienced an early recurrent DVT in the study by Grommes et al.⁷ Recurrent DVT occurred in 2 patients (29%) in the study by Oguzkurt et al.¹² Post intervention DVT was diagnosed in 2/56 (3.8%) of patients by Manninen et al.¹⁰ After 6 months recurrent DVT was 2% in the PEVI group compared to 15% in the anticoagulation alone group ($p=0.003$).¹⁵ In-

stent thrombosis was diagnosed in 1/11 (9%) of the cases in the study by Husmann et al.⁸ Early (<30 days) thrombosis of the stented iliac vein occurred in 3/21 stented limbs (14%); no late re-thrombosis was recorded in the study by Wahlgren et al.¹⁸ Rethrombosis was seen in 42/167(25%) limbs by Raju et al.; early (<30 days since stenting) in 10 limbs and late in 32 limbs.¹³ Seven out of 43 patients (16%) in the study by Nayak et al. experienced a stent occlusion during follow-up.¹¹ Re-thrombosis or re-occlusions occurred in 3/25 (12%) in the study by Dayal et al..⁶

Table 6.3 Suggested antithrombotic options

Study	Warfarin INR 2-3 for 3 to 6 months	Warfarin INR 2-3 for 12 months	Warfarin INR indefinitely	Antiplatelets	Graded compression stockings
1.AbuRahma 2001	All remaining patients	Patients after PE	All stented, patients with thrombophilia		
2.Dayal 2005			X		
3a.Sillesen 2005		X			X
3b.Bækgaard 2009		X			X
4.Husmann 2007	X				
5.Kölbel 2007	X				X
6.Raju 2009 earlier	only in case of thrombophilia: long term warfarin			Long term aspirin	
6.Raju 2009 later	For most participants: fondaparinux (4-6 weeks) and long term warfarin for selected patients				
7.Grommes 2011	X Idiopathic DVT: 6 months, provoked DVT: 3 months				
8.Oguzkurt 2010	X				
9.Titus 2010	X or Lovenox				
10.Wahlgren 2010	X			Aspirin 1 month (only for patients after surgery)	
11.Manninen 2011	X				X
12.Sharifi 2012	INR 2-3; no duration anticoagulant use mentioned			Aspirin at least 6 months+ clopidogrel 2 to 4 weeks for femoral/popliteal stents	X
13.Nayak 2012	Only those who were on anticoagulants prior to intervention			Aspirin for all participants	

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism

Patency rates

Long-term stent patency rates were assessed in 10/15 studies;^{4-6,8-10,13,14,17,18} primary, assisted primary patency and secondary patency rates 12 months after stent placement ranged from 54%, 72%, 83%¹³ respectively to 78%, 83%, 95%¹⁷ in (sub)groups of only stented patients. High patency rates in a (sub) population of only stented patients were reported by Titus et al. After 12 months of follow-up primary, assisted primary and secondary patency rates were 78%, 83% and 95% respectively. These high patency rates can possibly be explained by the fact that also patients without a prior DVT were included in this study.¹⁷

Pulmonary embolism

In 11/14 studies the incidence of PE was reported. Three studies reported an incidence of 0% PE in (sub) groups of only stented patients.^{11,13,17} Nayak et al. reported PE incidence of a subgroup of stented patients with PTS; the prevalence of inferior vena cava (IVC) filters was not reported,¹¹ Raju et al. reported zero PE in a population of stented patients with post-thrombotic chronic total occlusions; the prevalence of IVC filters was 10%¹³ and Titus et al. studied patients undergoing iliofemoral venous angioplasty and stenting; IVC filters were placed in case of very high PE risk.¹⁷ The population with the highest incidence of PE (7%), studied by Manninen et al. consisted of patients with acute iliofemoral DVT; in 9% of the patients an IVC filter was placed during the procedure.¹⁰ In the studies, performed by Abu Rahma (in endovascular intervention group), Grommes, Kölbel, and Oguzkurt 0% PE was reported in partially stented populations.^{4,7,9,12} The remaining studies by Bækgaard, Sillesen, and Sharifi (in endovascular intervention group) reported 6%, 2% and 1% of PE respectively.^{5,14,15}

Post thrombotic syndrome

PTS was assessed in 6/14 studies.^{8,11,13,15,17,18}; in only 2 studies^{8,18} the Villalta-Prandoni scale or the Venous Clinical Severity Score was used, both validated in different settings²⁴⁻²⁶ and subsequently endorsed by the International Society on Thrombosis and Hemostasis (ISTH).

One of these studies, a study performed by Husmann et al. assessed PTS in a population of only venous stented participants with May-Thurner syndrome and DVT: 10/11 stented patients with a target INR of 2-3 for the first 6 months had a Villalta score of 0 after a mean follow-up of 22 months. Duplex ultrasonography revealed no post-thrombotic changes in these patients; 1 patient reported mild PTS symptoms. Patients did not receive compression stockings after the intervention.⁸

Post-hoc analysis performed after a trial by Sharifi et al. suggested a protective effect of aspirin, on top of warfarin treatment (INR 2-3) in reducing the prevalence of PTS; relative risk (RR) of 0.37, confidence interval (CI) 0.19 to 0.74. In the endovascular intervention plus anticoagulation group 7% PTS was reported versus 30% in the anticoagulation alone group ($p<0.001$). All patients were advised to wear compression stockings; however, 6 months compliance was only 27%.¹⁵

A Chronic Venous Insufficiency Questionnaire was completed before and after the recanalization of 128 limbs in the report presented by Raju; significant improvements were noted concerning leg pain, sleep disturbance, effect on social activities and morale after the intervention. The hemodynamic parameters hand-foot pressure and ambulatory venous pressure showed no significant improvements. No graded compression stockings were prescribed post procedurally.¹³

Nayak et al. reported significant improvements after stent insertion for the variables any pain and any swelling as proxy for PTS; no compression stockings were prescribed after the procedure.¹¹ Titus et al. assessed by telephone whether symptoms overall had improved, had not changed, or became progressively worse: a distribution of 83%, 7% and 10% was found. In this study patients did not receive compression stockings.¹⁷

Finally, Wahlgren et al. reported Venous Clinical Severity scores before and after the intervention; the score dropped from 9.1 points preprocedural to 6.0 points postprocedural ($p<0.0001$). Patients were not advised to wear stockings post procedurally.¹⁸

Major bleeding

Finally we explored rates of major bleeding. Five studies reported 0% major bleedings during long term follow-up.^{11-14,17} In only 1 of these studies, performed by Nayak et al. all patients received aspirin, and anticoagulation was installed for those prior on warfarin; in the subgroup of stented patients no major bleeding occurred.¹¹

In another study by Raju et al. in which no major bleeding complications were reported only a part of the population received aspirin plus anticoagulation; the remaining part received anticoagulation or aspirin.¹³

In the remaining studies with 0% major bleeding complications all patients received warfarin for different time periods. The highest major bleeding scores (11%) were reported in a population, described by Abu Rahma et al, consisting of patients with iliofemoral DVT, of which 56% of the participants were stented. All patients were on warfarin (INR 2-3) indefinitely, without the addition of aspirin.⁴ Studies performed by

Bækgaard, Grommes, Kölbel and Manninen reported major bleeding rates of 1%, 8%, 8% and 4% respectively.^{5,7,9,10} In all these studies patients received only warfarin.

Discussion

Venous stenting is performed in case residual thrombi remain after CDT^{9,14} or lesions appear to be resistant to angioplasty.⁶ Overall, the evidence supporting the use of venous stents after a DVT in the iliofemoral area for improved short-term and long-term patency is convincing although of limited methodological quality. The lack of comparator studies is evident: only 2 studies^{4,15} of which 1 trial¹⁵ compared venous surgery plus anticoagulation to anticoagulation alone. In these studies the venous surgery group (not all stented) performed significantly better than the anticoagulation alone group in terms of patency,⁴ recurrent venous thromboembolism and development of PTS.¹⁵ Interestingly, in many cases thrombophilia screening is performed, but only on limited occasions type and duration of antithrombotic treatment are based on the outcomes of its findings.^{4,13} Post procedural antithrombotic therapy is not assessed separately as a potential factor for short-term and long-term failure or success of the stenting procedure in any of the presented studies. Based on this review we conclude that most stented patients receive warfarin only for the standard duration of the treatment of their underlying DVT; the fact that venous stents are inserted does not seem to affect this antithrombotic regime. This practice is in accordance with current ACCP guidelines.²¹ In only 4 studies patients received additional antiplatelet therapy after CDT and/or PMT and stent placement.^{11,13,16,18} In 1 study clopidogrel at 75 mg per day for 2-4 weeks was administered to exclusively stented patients.¹⁶ Combination therapy, consisting of anticoagulant and antiplatelet therapy or dual antiplatelet therapies (aspirin plus clopidogrel) may theoretically be an interesting option. It is conceivable that antiplatelet agents could provide additional protection against the formation of thrombi after venous stenting of the iliac vein.²⁷ Shear forces are a major determinant of platelet deposition in thrombi; in the venous system usually low-flow, low-shear conditions exist and occurring thrombi are likely platelet poor and fibrin rich. In the iliac vein however, due to thickening and scarification of the vessel wall after a DVT and/or external compression, shear forces are in some cases anticipated to be nearly identical to the arterial system.²⁷ In experimentally induced thrombi in these venous segments, indeed platelet rich thrombi occurred and these platelets were in an activated state.²⁷ However, aspirin, clopidogrel, and aspirin plus clopidogrel did not

significantly reduce stent thrombosis in an experimental model neither did they prevent platelet accumulation, while anticoagulant therapy did reduce thrombosis.²⁷

The lowest patency rates were reported by Wahlgren, Dayal and Raju:^{6,13,18} Low patency was combined with high rates of recurrent DVT (14%, 12% and 25% respectively). In these studies acute and chronic DVT, and in the case of Dayal also DVT at unusual sites were included. As far as the antithrombotic regimen that was applied in these studies is concerned, no beneficial effect was observed by the additional aspirin administration in those stented.^{13,18} The low patency rates in these studies can at least partially be explained by the fact that patients with chronic DVT and with total occlusions were included. In the study by Nayak aspirin was prescribed to all, and additional warfarin to those with previous use of warfarin; the recurrence rate was 16%.¹¹ Besides the antithrombotic effects also anti-inflammatory effects could play a role while using antiplatelet agents. There could be an additional effect of aspirin on top of warfarin treatment for the reduction of the prevalence of PTS, as was suggested by the post-hoc analysis performed by Sharifi et al.¹⁵ that showed a significant reduction of the incidence of PTS in patients on aspirin.

The safety of antiplatelet therapy in combination with anticoagulation in patients after venous stenting is something to be considered. Limited data are provided by 2 studies by Nayak and Raju, wherein aspirin plus warfarin therapy was applied and 0% major bleedings were reported,^{11,13} the remaining 2 studies in which the patients received antiplatelet plus anticoagulant therapy also no major bleedings were reported.^{15,18} Therefore in terms of safety, the addition of aspirin to the antithrombotic regimen does not seem to pose a large problem, at least on the short term in the patients selected in these studies.

The highest primary patency rates were reported in studies performed by Manninen, Sillesen and Abu Rahma;^{4,10,14} all patients received warfarin with a target INR 2-3 for the standard duration for the underlying DVT, and no antiplatelet therapy was administered. In all three studies only patients with acute DVT were included; fresh thrombi probably resolve better after CDT than sub acute thrombi.²⁸ Also low rates of recurrent thrombosis were reported in these studies. These 3 studies were all awarded with 4/5 stars for study quality; we therefore can assume that the study findings are trustworthy. Kölbel also reported low rates of recurrent DVT and PE.⁹ A very high percentage (68%) of the total study population was diagnosed with thrombophilia; this did however not influence antithrombotic management.

Anticoagulants likely play a more important role than antiplatelet agents in the prevention of re-stenosis in venous stented patients with a prior DVT.^{2,21} Recurrent venous thrombosis is primarily caused by increased thrombin generation,²⁹ therefore anticoagulants likely have better antithrombotic properties in patients with venous

stents after a DVT than antiplatelet drugs. The major bleeding risk of long-term warfarin use with a target INR of 2-3 was estimated at 1.3% per year.³⁰ The rates of major bleeding reported in this review are in a higher range between 8-11%. The additional bleeding risk is mainly due to the stenting procedure. This may be an acceptable risk if stenting would lead to clearly better outcomes.

Based on the available evidence in this review no firm conclusions regarding the association between the duration of antithrombotic therapy and the study outcomes can be drawn. A major limitation of this study is the fact that no meta-analysis could be performed. The quality of the included studies was sub optimal; single armed cohort studies with mostly a small sample size formed the majority in this review. Applicability of the review may be affected by the fact that most studies assessed patient groups undergoing CDT and/or PMT of which only a part underwent stenting; subgroups consisting of only stented patients could be assessed in only a few cases. The most important factors contributing to a favorable outcome, high patency and low recurrence rate are mainly dependent on the location of the thrombus and the age of the thrombus. Thrombophilia is not a discriminating factor for success. Anticoagulant therapy for the duration of the underlying thrombotic lesions seems to be sufficient.

The conclusion of this systematic literature review is that antithrombotic therapy does not seem to influence any of the outcomes in patients with venous stenting after DVT: patency, PTS, PE, recurrent DVT or restenosis and bleeding. The main drivers for the outcome are the location of the DVT, the age of the thrombus and the stenting procedure itself.

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Appendix 6.1 The search strategy for MEDLINE

((stents[MeSH Terms] OR stent[MeSH Terms] OR angioplasty[MeSH Terms] OR Percutaneous recanalization OR endovascular interventions) AND (venous ulcer[MeSH Terms] OR venous ulcers[MeSH Terms] OR venous insufficiencies[MeSH Terms] OR venous insufficiency[MeSH Terms] OR "postthrombotic syndrome"[MeSH Major Topic] OR deep venous thromboses[MeSH Terms] OR deep venous thrombosis[MeSH Terms]) AND (agents, anticoagulant[MeSH Terms] OR anticoagulant agents[MeSH Terms] OR anticoagulant drugs[MeSH Terms] OR anticoagulants[MeSH Terms] OR drugs, anticoagulant[MeSH Terms] OR blood platelet aggregation inhibitors[MeSH Terms] OR agents, antiplatelet[MeSH Terms] OR antiplatelet agents[MeSH Terms] OR antiplatelet drugs[MeSH Terms] OR drugs, antiplatelet[MeSH Terms])) OR ((stent OR angioplasty OR Percutaneous recanalization) AND (venous ulcer[MeSH Terms] OR venous ulcers[MeSH Terms] OR venous insufficiencies[MeSH Terms] OR venous insufficiency[MeSH Terms] OR "postthrombotic syndrome"[MeSH Major Topic] OR deep venous thromboses[MeSH Terms] OR deep venous thrombosis[MeSH Terms]) AND (anticoagulant OR anticoagulant agents OR anticoagulant drugs OR anticoagulants OR blood platelet aggregation inhibitors OR Antiplatelet OR antiplatelet agents OR antiplatelet drugs))

Limits Activated MEDLINE: English

Appendix 6.2 Newcastle-Ottawa quality assessment scale for cohort studies (selection of 5 items)

Selection

- 1) Representativeness of the cohort
 - a. truly representative of the population of patients undergoing venous stenting in the iliofemoral area after a first or recurrent DVT; all participants stented *
 - b. somewhat representative of the population of patients undergoing venous stenting in the iliofemoral area after a first or recurrent DVT; not all participants stented *
 - c. additional inclusion criteria and not all participants stented.
 - d. no description of the derivation of the cohort
- 2) Ascertainment of exposure
 - a. secure record (e.g. surgical records) *
 - b. structured interview *
 - c. written self report
 - d. no description

Outcome

- 3) Assessment of outcome
 - a. independent blind assessment *
 - b. record linkage *
 - c. self report
 - d. no description
- 4) Was follow-up long enough for outcomes to occur
 - a. yes (≥ 24 months (mean or median)) *
 - b. no
- 5) Adequacy of follow-up of cohorts
 - a. complete follow-up - all subjects accounted for *
 - b. subjects lost to follow-up ($< 5\%$) unlikely to introduce bias or description provided of those lost *
 - c. follow-up rate $< 95\%$ and no description of those lost
 - d. no statement

Chapter 7

Quality of anticoagulant therapy and in-stent thrombosis in patients with venous stents

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Cees H.A. Wittens, Arina J ten Cate-Hoek

Submitted

Abstract

Introduction

In patients with venous outflow obstruction following iliofemoral deep vein thrombosis (IFDVT) stenting of venous tracts to prevent or alleviate post thrombotic syndrome (PTS) is applied with increasing frequency. Up till now the association of quality of anti-thrombotic therapy and effectiveness of stenting has not been studied explicitly. The impact of the quality of anticoagulant therapy with vitamin K antagonists (VKA) expressed as time within therapeutic range (TTR) and proportion of INR values <2.0 on in-stent thrombosis is currently unknown.

Methods

Seventy-nine patients with venous stent placement after acute or chronic iliofemoral or caval DVT were included in this study. All patients used VKA after the intervention. TTR was calculated according to the linear interpolation method. In-stent thrombosis was assessed by the use of duplex ultrasound. Survival analysis (Cox regression, Kaplan Meier curves) was used to analyze the data.

Results

The average TTR was 46.4% (SD 20.8); the average proportion of INR measurements <2.0 was 9.5% (SD 11.6). Increasing TTR was associated with a lower risk of in-stent-thrombosis. The multivariable adjusted analysis resulted in a hazard ratio of 0.940 (95% CI 0.890–0.993) per 1% increase in TTR. An increase of the proportion of INR values <2.0 was not significantly associated with the outcome in-stent thrombosis; HR per 1% increase in proportion of 1.018 (95% CI 0.957–1.084).

Conclusions

We conclude that an increase of TTR offers protection against in-stent thrombosis. The proportion of INR <2.0 , although expected to be an important predictor for in-stent thrombosis, could not be identified as a risk factor in this study. An overall low average TTR of 46.4% (SD 20.8) was recorded, possibly due to the relative short follow-up in combination with the initiation phase of VKA, leading to unstable INR values.

Introduction

Post thrombotic syndrome (PTS) develops in over 50% of patients with iliofemoral deep venous thrombosis (IFDVT).¹ Conservative treatment regimens comprising of a combination of compression therapy, mobilization and oral anticoagulants, up till now mainly vitamin K antagonists (VKA), result in suboptimal outcomes in these patients. Over the last 2 decades the use of percutaneous transluminal angioplasty (PTA) and stenting of venous outflow obstructions of the iliofemoral and caval veins has gained more attention. PTA and stenting appears to be effective in terms of objective and subjective clinical improvement of PTS symptoms and has been characterized by good mid- to long-term patency rates in mainly observational studies.²⁻⁸ The treatment usually consists of guide-wire recanalization of the obstructed venous segments and placement of one or more stents, followed by anticoagulant therapy with VKA for at least 3 months. In acute DVT patients in whom catheter directed thrombolysis (CDT) is applied, additional venous stenting immediately following thrombolysis is often indicated in case of underlying venous pathology, such as iliac vein compression syndromes, which is thought to be the underlying cause of thrombosis in these patients.⁹

So far the contribution of the quality of anticoagulant therapy, to the effectiveness of venous stenting has not been evaluated.¹⁰ The current guidelines issued by the American College of Chest Physicians (ACCP) do not specifically advise on anticoagulation therapy after venous stenting mainly for lack of evidence.¹¹ In the literature a variety of antithrombotic therapies are suggested after venous stent placement for chronic venous obstruction or directly after CDT in acute thrombosis; anticoagulant therapy varying from 3 months to 1 year with target range INR of usually 2 to 3 is prescribed, sometimes in combination with antiplatelet therapy.¹⁰ While time within therapeutic range (TTR) of VKA therapy in acute DVT is known to have substantial impact on recurrent DVT,^{12,13} the role of the quality of TTR during VKA therapy in preventing re-occlusion after venous stenting remains unclear. In addition INR values <2.0 are an established risk factor for recurrent venous thromboembolism (VTE),¹³ as well as for PTS.^{14,15} Even though the contribution of the quality of anticoagulation therapy will therefore likely also play a role in the effectiveness of venous stenting, so far no study has analyzed TTR and proportion of INR values <2.0 in patients undergoing venous stenting in acute DVT or for chronic venous obstruction in relation to stent patency.

We therefore evaluated the contribution of the quality of anticoagulation control during treatment with VKA calculated with the linear interpolation method. In addition we assessed the impact of the proportion of INR values <2.0 on in-stent

thrombosis in chronic PTS patients on long-term anticoagulation with iliofemoral and or caval venous stents placed in patients with chronic PTS.

Methods

Patient selection

During the period from March 2009 until January 2013 108 patients, referred to the Department of Vascular Surgery in the Maastricht University Medical Center, the Netherlands for venous stent placement after acute or chronic iliofemoral or caval DVT, and who had used VKA for at least 3 months after the intervention and had at least 1 year of follow up data available were invited to participate in the current study. Patients with symptomatic deep venous obstruction without a history of DVT; i.e. cases of iliac vein compression syndrome (such as May-Thurner syndrome) were not eligible. Seventy-nine patients of whom 82.4 % used VKA prior to the intervention, gave informed consent to retrieve patient data from their anticoagulation clinic records. All data, except data concerning anticoagulation therapy were collected prospectively. Institutional review board approval was obtained (METC 14-4-081).

Baseline work-up

All patients were scheduled for a standardized work-up, consisting of clinical evaluation, duplex ultrasound (DUS) and magnetic resonance venography (MRV) prior to the intervention. The primary objective using DUS is the assessment of signs of recanalization and/or flow impairment, luminal narrowing, vein wall thickening and any possible external compression on vein segments, such as iliac vein compression syndrome. During follow-up DUS was used to assess patency of stented venous tracts and vein segments proximal and distal of the stents, as well as the configuration of the stents themselves. The LET score, a classification that stratifies patients into 4 groups (I-IV) in accordance to the location of the most proximal thrombus, was used to classify patients.¹⁶ With MRV the extend and severity of intraluminal post thrombotic changes and collateralization, and the locations of trabeculae, longitudinal vertical strands attached to the vein wall that indicate PTS, were recorded.¹⁷

Stent placement

All procedures were performed under general anesthesia in a dedicated angiosuite. In patients using VKA at the time of intervention, the procedure was performed under full anticoagulation; i.e. coumadins were not stopped in the days preceding the

stenting procedure if INR was <4 . In patients not using anticoagulation at the time of intervention, 5.000 IU of unfractionated heparin was administered at the start of the procedure, and another 5.000 IU was given at the discretion of the treating physician in case of prolonged duration of the intervention. Venous access was obtained via the femoral vein under ultrasound guidance, generally at least 15 cm distally to the deep femoral inflow. With the use of various guide wires recanalization into the vena cava inferior was performed.¹⁸ As only stented patients were included in this study, the success rate for recanalization was set at 100%. Following recanalization pre-dilatation, i.e. PTA, of the obstructed vein segments was performed in the iliofemoral tract. Following pre-dilatation the affected vein segments were stented. The proximal and distal landing zones of the stents were placed in "healthy vein". Self-expendable stents, ranging in size of 12-16mm in the iliofemoral tract, and 25mm in the caval tract, were used in all cases (sinus XL, sinus Venous and sinus XL-flex, Optimed, Ettlingen, Germany and Zilver Vena (Cook, Galway, Ireland). For a small number of bilaterally affected patients balloon expendable stents were used to reconstruct the confluens of the vena cava ((AndraStent, Andramed, Reutlingen, Germany).¹⁹

In patients using VKA prior to the intervention, anticoagulant therapy was continued for at least 6 months following the intervention. All other patients received LMWH directly after the procedure, and were started on VKA on the first day post-intervention. Stenting procedures were performed for three different indications: CDT + stenting after acute DVT, stenting after (chronic) PTS, and stenting with endophlebectomy and AV fistula after (chronic) PTS.

Follow up and outcomes

Patients were assessed at 2 weeks, 6 weeks, and 3, 6 and 12 months after the intervention and annually thereafter, or earlier when necessary, for a regular check-up. A standardized clinical assessment by a trained physician was performed and DUS to assess patency and possible stent configuration problems (kinking, migration, fracture, changes in orientation). In-stent thrombosis was defined as thrombosis with 100% occlusion of the treated vein. An endpoint for the study was reached when VKA administration was stopped, or when the last patency measurement was performed or when in-stent thrombosis occurred.

Anticoagulation

Patient records were retrieved from patient's individual anticoagulation clinics. Patient records included INR values, start and stop dates of VKA, indications for VKA therapy, target INR values, type of VKA (acenocoumarol, fenprocoumon) and

instructions on the need to administer low molecular weight heparin (LMWH) in case of INR <2.5. The time within the therapeutic range (TTR) was calculated for all participants using the linear interpolation method as proposed by Rosendaal et al.²⁰ This method assumes a linear relationship in time between 2 INR measurements. The first INR taken into account after the start of VKA treatment had a value of 2.0 or higher and was preceded by another INR measurement of 2.0 or higher. Hereafter all INR values were included for TTR calculation until the time the outcome occurred or the last patency measurement was performed. Furthermore the proportion of INR measurements with a value below 2.0 was calculated for each patient. In our analysis we also included the variables TTR and proportion of INR values <2.0 restricted to the first 8 weeks post-surgery to investigate the effect of the quality of anticoagulation of the (re)initiation phase on in-stent thrombosis. Some patients switched during the follow up from VKA to rivaroxaban or antiplatelet therapy; this was recorded as well.

Statistical analysis

Descriptive statistics were used to determine baseline characteristics. Continuous variables are reported as means, their standard deviations (SD); categorical data are presented as percentages. Student's T-tests and Chi² tests were performed to compare groups. Kaplan Meier curves are presented for the comparison of the outcome in-stent thrombosis between the group with a TTR ≤ the median value of the group without in-stent thrombosis (control group) and a TTR > than median control group. To compare groups log rank tests were performed. The Cox regression was used to express the association between the independent variables TTR and percentage of INR measurements <2.0 separately, corrected for possible confounders in relation to the outcome in-stent thrombosis. Interactions between TTR, proportion of INR values <2.0 and INR target range (2.5–3.5 and 3.0–4.0) were assessed. Person time was calculated from the time of the intervention up to the time when the outcome of interest occurred, the patient stopped using VKA or to the time of the last patency assessment was performed. Risks are presented as hazard ratios (HR) with accompanying confidence intervals (CI) or p - value. We used two ways to determine which variables finally entered the multivariable-adjusted models: 1) the potential confounder is predefined, i.e. in literature the association between the exposure of interest and in stent-thrombosis was described; or 2) the potential confounder is associated with in-stent thrombosis (p-value <0.20). We selected the variables age at inclusion, gender, LET score, LMWH administration if INR <2.5 (yes/no) and VKA type (acenocoumarol, fenprocoumon). The proportional hazards assumption was tested for all variables. The analyses were restricted to patients with chronic iliofemoral DVT; we

therefore excluded 9 patients with acute DVT + compression syndrome, because these patients have a different pathology and the effect of TTR on in-stent thrombosis therefore probably is different. SPSS version 22 was used for all analyses.

Results

Patient characteristics are detailed in Table 7.1. The average age at baseline was 41.5 years (SD 14.3 years) and 34.2% were male. We found an average TTR of 46.4% (SD 20.8) for the whole group. In the total population 20.3 % of patients developed in-stent thrombosis; 15.0 % were diagnosed with in-stent thrombosis in the group of PTS patients with an INR target range of 2.5–3.5, and 25.0 % acquired in-stent thrombosis in the group of patients with range 3–4, ($p=0.27$).

Table 7.1 Patient characteristics

age	79	41.5 (SD 14.3)
Sex	79	
Male	27	34.2 %
Female	52	65.8 %
Thrombophilia		
No test performed	53	67.1 %
No thrombophilia	13	16.5 %
Factor V Leiden	11	13.9 %
Antiphospholipid syndrome	1	1.3 %
Factor V Leiden + prothrombin G20210A mutation	1	1.3 %
Underlying pathology		
Acute DVT with compression syndrome	6	7.6 %
Post thrombotic syndrome	73	82.4 %
Most proximal segment LET score according to DUS		
LET III	53	67.1%
LET IV	13	16.5%
No LET score available	13	16.5%
Outcomes		
<i>In stent thrombosis</i>		
No	63	79.7 %
Yes	16	20.3 %

Abbreviations: DUS, duplex ultrasonography; DVT, deep venous thrombosis; LET, lower extremity thrombosis

TTR was higher for patients with INR values included during a period longer than 408 days (median follow up) compared to those with a shorter period of INR values available; 56.7% and 33.3% respectively ($p<0.001$). For all anticoagulation characteristics: see Table 7.2.

Table 7.2 Anticoagulation characteristics for all patients, patients with a TTR below and patients above the median TTR of control group (47.9%)

Variable	Number	All patients	TTR ≤47.9% (median controls)	TTR >47.9% (median controls)	p-value	INR Range 2.5–3.5	INR Range 3.0–4.0	p-value
INR range								
2.5-3.5	40	48.1%	16	18	p=0.43			
3.0-4.0	36	43.0%	19	11				
3.5-4.5	3	3.8%	1	1				
VKA								
acenocoumarol	46	55.7%	22	18	p=0.93	25	20	p=0.64
fenprocoumon	33	40.5%	14	12		15	15	
TTR	66	46.4% (SD 20.8)	31.9% (SD 13.0)	63.9% (SD 13.6)	p<0.001	49.1%	43.2%	p=0.27
TTR (in patients with follow up >408 days (median)	33	56.7%			p<0.001			
TTR (in patients with follow up <408 days (median)	33	33.3%						
Mean % INR < 2	66	9.5% (SD 11.6)	13.8%(SD 12.0)	4.4% (SD 8.7)	p<0.001	12.0% (SD 12.5)	6.0% (SD 8.5)	p=0.03
INR tests in range	66	41.9% (SD 18.4)	30.1% (SD 13.7)	54.4%(SD 15.9)	p<0.001	45.0% (SD 20.3)	36.4% (SD 16.5)	p=0.07
Average INR	66	3.2 (SD 0.47)	3.1 (SD 0.5)	3.2 (SD 0.3)	p=0.52	3.0 (SD 0.4)	3.3 (SD 0.5)	p=0.002
LMWH if INR <2.5								
No	52		22	18	p=0.93	27	22	p=0.46
yes	27		14	12		12	14	

Abbreviations: LMWH, low molecular weight heparin; TTR, time within therapeutic range; VKA; vitamin K antagonists; LMWH , low molecular weight heparins

Survival analysis was performed using Kaplan Meier curves, log rank tests and Cox survival analysis. In all these analyses person time was calculated only for the patients using VKA; patients were censored at the moment they stopped with VKA use (stop anticoagulant use altogether or start of another type of antithrombotic agent (e.g. antiplatelet therapy or direct FXa inhibitors).

In Figure 7.1 and 7.2 Kaplan Meier curves are depicted for the outcome in-stent thrombosis with cut-offs defined at the median of the respective control groups (patients without in-stent thrombosis); Figure 7.1 cut-off for TTR at $\leq 47.9\%$, and Figure 2 cut-off for proportion INR values < 2.0 at $\leq 7.7\%$. The Log rank tests resulted in $\chi^2=5.54$, $p=0.02$ and $\chi^2=0.03$, $p=0.86$ for figure 1 and 2 respectively.

Figure 7.1 Kaplan Meier analysis. Outcome: in-stent thrombosis for groups TTR $<47.9\%$ (median controls) and TTR $\geq 47.9\%$

Abbreviations: TTR, time within therapeutic range

Figure 7.2 Kaplan Meier analysis. Outcome: in-stent thrombosis for groups proportion of $INR < 2.0 \leq 7.7\%$ (median controls) and proportion of $INR < 2.0 > 7.7\%$

The analyses using the Cox regression are presented in Table 7.3. A linear decrease of the risk of in-stent-thrombosis associated with increasing TTR was found in all three models: the univariable, the age and sex adjusted model and in the multivariable adjusted analysis; respective HR per 1% increase in TTR were 0.954 (95% CI 0.920-0.988), 0.943 (95% CI 0.903-0.985) and 0.940 (95% CI 0.890-0.992). For INR values lower than 2.0 multivariable adjusted analysis resulted in a HR per 1% increase in proportion of 1.018 (95% CI 0.957-1.084). In the analysis of both determinants we entered the same possible confounders in our models. Pearson correlations between the independent variables TTR and proportion of INR values < 2.0 were determined for the groups with INR ranges 2.5-3.5 and 3.0-4.0 (only PTS patients); -0.55 ($p=0.004$) and -0.27 ($p=0.17$) respectively. Interactions between TTR, proportion of INR values < 2.0 and INR target range (2.5-3.5 and 3.0-4.0) were calculated: $p=0.08$ and 0.47 respectively. To investigate the effect of the (re) initiation phase on in-stent thrombosis we calculated the TTR and proportion of INR values < 2.0 for the first 8 weeks post-surgery. Overall non-significant results were found; in models using the same confounder set as described earlier the increase of 1% in TTR resulted in a HR of 1.023 (95% CI 0.980-1.069); an increase of 1% in the proportion of INR values < 2.0 resulted in a HR of 0.928 (95% CI 0.848-1.015). The proportional hazard assumptions were not violated for TTR and proportions of INR values < 2 ; therefore the effect of these independent variables may be assumed constant over time; also for all possible confounders this assumption was not violated.

Table 7.3 Univariable, age and sex adjusted and multivariable adjusted hazard ratios for in stent thrombosis in patients with PTS according to TTR and percentage INR<2

	Univariable: HR (95% CI)	Age sex adjusted: HR (95% CI)	Multivariable adjusted ^a : (HR (95% CI)
TTR (per 1% increase)	0.954 (0.920-0.988)	0.943 (0.903-0.985)	0.940 (0.890-0.992)
TTR (per 10% increase)	0.624 (0.434-0.886)	0.556 (0.361-0.860)	0.539 (0.312-0.922)
INR <2 (per 1 % increase	1.024 (0.969-1.083)	1.033 (0.975-1.096)	1.018 (0.957-1.084)
INR <2 (per 10% increase	1.268 (0.730-2.220)	1.384 (0.776-2.501)	1.195 (0.664-2.240)

^a Adjusted for: Age at baseline, sex, LET score, LMWH administration if INR <2.5 (yes/no), VKA: acenocoumarol or fenprocoumon. Abbreviations: HR, hazard ratio; PTS, postthrombotic syndrome; TTR, time within therapeutic range

Discussion

In this study we found that the quality of anticoagulant therapy with vitamin K antagonists has a strong effect on in-stent thrombosis in patients after iliofemoral stent placement. We identified TTR as the most important predictive variable that reflects the quality of anticoagulant therapy and its associated risk for in-stent thrombosis. A 10% increase in TTR resulted in a risk reduction for in-stent thrombosis of 46.1%. In case of in-stent thrombosis also the proportion of INR values <2.0 are expected to be of interest. And although not significant, an increase of 10% in proportion of INR values <2.0 was associated with an 18.4% increase in in-stent thrombosis. The reason for this lack of significance may be due to the relatively small sample size and the lack of contrast in the population. LMWH was prescribed for INR<2.5 in both patients without in-stent thrombosis and patients with a thrombotic event in equal proportions, which may have further obscured possible differences. In addition the overall percentage of INR values <2.0 was low in this population, compared to other studies.¹³⁻¹⁵

The TTR was significantly higher in patients without in-stent thrombosis and remained an independent predictor of thrombotic complications after correction for possible confounders. Interestingly, the proportion INR <2.0 between the groups with TTR below and above median of controls differs considerably (13.8% (SD 12.0) versus 4.4% (SD 8.7) and is highly significant, indicating that the effect of TTR can be explained at least partially by the fact that a low TTR results in increased proportions of sub therapeutic INR values. Furthermore, strong correlations between TTR and proportion of INR values <2.0 were observed, especially in the group with INR range 2.5-3.5. Besides the association between TTR and sub therapeutic INR values, another phenomenon with regard to TTR and in-stent thrombosis might play a role. Patients with low TTR experience more periods of increasing/decreasing effects of VKA; during

periods of increasing effects the relatively low concentrations of active procoagulants protein C and protein S compared to high concentrations of active procoagulant proteins FX and prothrombin might induce a prothrombotic state irrespective of the INR value.

Compared to other studies low rates of TTR were found in our, overall young study population.¹³ This can be explained at least partially by the fact that the study population consists of patients with a relatively short treatment period over which TTR was calculated. This, combined with the fact that in patients with shorter follow-up lower TTR values are recorded because (re) initiation after surgery of VKA therapy, leads to unstable INR values during the first 6 weeks and results in low TTR.²¹

The sample size of our study was small. This can be explained by the fact that venous stenting is a relatively new treatment modality, and is not yet performed on a large scale. There are however also several strengths of our study, including the prospective design, the clear definition of endpoints, an objectively documented recurrence, and regular follow up of patients.

Based on the results of our study we conclude that following a stenting procedure in patients with PTS, the quality of anticoagulant treatment is of paramount importance. The fact that an overall low average TTR was recorded in this specific peri-procedural setting may indicate the need for stricter monitoring of anticoagulant treatment or for alternative treatment modalities.

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Chapter 8

General discussion

In this chapter, the main findings of this thesis will be discussed. Three topics are discussed: first, a study on clinical decision support (CDS) with regard to thromboprophylaxis in non-surgical hospital patients; second, safety and efficacy issues of bridging anticoagulation and finally, safety and efficacy issues of anticoagulation after venous stenting. All safety issues concern the risk of minor or major bleedings; efficacy aspects involve the risk of thromboembolism (TE), both venous and arterial.

Summary

In **Chapter 2** practical aspects of thromboprophylaxis in hospitalized medical patients were assessed. The adherence to guidelines was measured before and after introduction of a CDS system. Contrary to expectations from literature no improvement was observed in guideline adherence towards antithrombotic prophylaxis.

In **Chapter 3** a systematic literature review is presented, evaluating bridging therapy compared to vitamin K antagonists (VKA) continuation and cessation in terms of bleeding and TE risk. The review yields 2 findings: 1) no conclusion can be drawn regarding the efficacy of bridging therapy because the low incidence of thromboembolic events; 2) bridging anticoagulation results in a higher bleeding risk compared to perioperative continuation of VKA in surgical interventions involving pacemaker/defibrillator implantations or replacements.

An observational registry assessing the practice of perioperative bridging of anticoagulation showed limited guideline adherence resulting in prolonged bridging procedures, excess treatment of patients and high bleeding rates (**Chapter 4**).

An explorative study assessing the mechanisms underlying bridging therapy showed that whereas cessation of VKA normalized the INR value at the day of surgery, in a number of individuals clinically relevant residual anti-Xa activity was measured on the day of the intervention. In spite of this, we did not find a clear-cut association between residual anti-Xa activity and post interventional bleeding in this small series of patients. A detailed analysis of coagulation proteins yielded a pattern of procoagulant effects involving 3 distinct elements: a marked effect of FXI in the thrombin generation assay, a reduced activity of the APC pathway and a postoperative rise in FVIII and fibrinogen (**Chapter 5**).

A systematic review of studies evaluating the effectiveness of venous stenting in relation to postthrombotic complaints exposed an apparent lack of concern for antithrombotic therapy in relation to the stenting procedures, resulting in a marked

variation in anticoagulant management strategies, both in duration and intensity. **(Chapter 6)**

To investigate the importance of anticoagulation in relation to in-stent thrombosis after venous stenting a study was performed in patients undergoing venous stenting. When analyzing time in the therapeutic range (TTR) in patients treated with VKA, we observed that higher TTR, a measure of quality of anticoagulation, offers better protection against in-stent thrombosis **(Chapter 7)**.

Clinical decision support for thromboprophylaxis

Findings in perspective

Deep venous thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), is an underestimated health problem. Different studies demonstrate that in only 30-50% of the patients indicated for prophylaxis appropriate measures are indeed taken.¹⁻³ Thromboprophylaxis is underused in day-to-day practice, while LMWH has proven to be very effective in the prevention of VTE in surgical and non-surgical patients.⁴⁻⁶ CDS, varying from simple electronic alerts to extensive fill-in lists of (weighed) risk factors, integrated in digital patient's records, are tools that may potentially improve guideline adherence and reduce the risk of in-hospital VTE. We found no improvement in guideline adherence towards antithrombotic prophylaxis in medical patients after the introduction of CDS in our pilot study, performed in the Maastricht University Medical Center. Guidelines were followed in 59.4% both before and after the introduction of CDS. There was however a non-significant shift towards over-treatment, which may be indicative of higher prophylaxis awareness. The finding that CDS did not result in higher guideline adherence is not coherent with results presented in other studies. The introduction of CDS is in several studies associated with increased rates of per protocol administration of VTE prophylaxis, increased rates of administration of VTE prophylaxis in general⁷ and even with reduced rates of VTE.⁸ The observed lack of improvement in adherence in this pilot study could, at least partially, be caused by the suboptimal use of CDS. Final use of CDS varied between 23.7% and 57.4% for the different wards. A barrier towards implementation of CDS could have been the additional time investment needed as indicated by physicians; moreover, time consuming separate login procedures were required in order to enter CDS. Doubts whether CDS was based on solid evidence, uncertainty about the correctness of CDS advices for 'complex' patients, experienced difficulties due to the introduction of CDS and deviation from

CDS advice caused by patient's preferences as indicated in the questionnaire presented to participating physicians, also might have contributed to the perceived lack of improvement in adherence. CDS can be a helpful tool in VTE prophylaxis management if the barriers as described above are broken down. An important condition for successful implementation is that all parties involved in patient care (physicians, ICT staff, hospital management) need to be convinced of the importance of CDS and that sufficient financial resources are available to implement a workable system.

Methodological issues

Only 128 patients participated in this pilot study and no follow-up VTE incidences were assessed. Therefore the possible association with the incidence of VTE could not be investigated. Secondly, VTE risks for patients at baseline (T0) were determined using a local protocol that did not include a risk score for bleeding. The risk assessment model (RAM) used at T1 included a calculated score for bleeding risk. This could have led to a difference in risk perception. The fact that no link was provided to the ordering system may have been the most important barrier, resulting in the limited impact of CDS in this study.

Clinical implications

The use of CDS can, if used consistently lead to improved guideline adherence and even to reduced incidence of VTE. The long-term successful effect of CDS requires training in CDS use on a regular basis to avoid a fade-out effect; this training should include an overview of the strengths of available evidence and the validation procedure of the risk scores. Also the importance of CDS in terms of avoidable VTE cases should be made clear. Only if the time investment is limited (swift log in procedures, short lists with risk factors and risk factors like age, BMI, blood results filled in automatically) a significant long-term effect of CDS can be expected. In the context of our study a questionnaire evaluating CDS use was filled in by the participating physicians: 40 % had the opinion that a direct link to the ordering system would lead to an improvement; 80% questioned whether the CDS was evidence based. Bates et al. reviewed studies in which CDS systems used in different fields of expertise were evaluated and found that "speed" is a key factor for success; slow systems are ineffective.⁽⁹⁾ A successful CDS VTE prevention system in which a direct link to the ordering system was provided was described in a study performed by Umscheid et al.⁷

Future implications

CDS supported prophylaxis is potentially superior to conventional prescription of thromboprophylaxis. In some studies CDS was effective, other studies failed to demonstrate the effect of CDS on guideline adherence. Therefore, future research should focus on the conditions needed for the implementation of an effective CDS system, such as user-friendliness and user-confidence in the correctness of the CDS generated advice.

Bridging anticoagulation

Findings in perspective

We reviewed the efficacy and safety of bridging therapy systematically.¹⁰ The most important finding of our study is that no conclusion can be drawn regarding the efficacy of bridging therapy. Overall TE incidence was low, in some studies zero. Similar findings were reported in other reviews^{11,12}. We performed a meta-analysis assessing the risk of minor bleeding, major bleeding and overall bleeding in pacemaker/implantable defibrillator surgery. Analyses of overall bleeding resulted in a relative risk (RR) of 3.03 (95% confidence interval (CI), 1.86-4.95). A recent meta-analysis of patients undergoing pacemaker/implantable defibrillator surgery performed by Yang et al. reported that a strategy of warfarin continuation compared to bridging anticoagulation actually reduced the risk of bleeding (odds ratio (OR) 0.31 (95 % CI, 0.18-0.53)).¹³ The recently published BRIDGE study found in patients with atrial fibrillation undergoing overall low surgical stress inducing interventions that discontinuation of warfarin therapy was noninferior to LMWH bridging in terms of arterial TE and superior in terms of major bleeding.¹⁴ These data raise several questions that cannot be easily answered at this stage: 1) does the lack of advantage in the recent BRIDGE study effectively rule out application of bridging in all surgical procedures (including high thrombosis risk procedures and high risk patients)? 2) is LMWH effective, but are we over-dosing, given the residual anti-Xa levels on the day of the intervention and the apparent and in several analyses observed elevated bleeding risk? Or is bridging started too close to surgery? In an exploratory study on bridging anticoagulation we tried to get a better insight into the different mechanisms operational around the intervention. Thus, in a small series of patients we were able to collect blood samples over 9 consecutive days and found that on the day of the intervention LMWH associated anti-Xa levels >0.05 IU/ml, were still detectable in 84.6% of the population. Possible contributors to this residual anticoagulant activity

were reduced renal clearance and BMI >30 kg/m².⁽¹⁵⁾ Based on our study one may speculate that the timeframe of 24 hours between the last dose of LMWH and surgery should be extended. In a study performed by Douketis et al. residual anti-Xa effects of >0.10 IU/ml just before surgery were observed in 16.4% of the population¹⁶ This residual anti-Xa effect might play a contributory role in postoperative bleeding; a systematic review showed that patients bridged with therapeutic doses of LMWH had a significantly increased risk of bleeding compared to patients bridged with prophylactic/intermediate doses of LMWH.¹⁷ These data show the uncertainty that pertains to both the time interval of bridging to surgery and the actual doses that should be employed. Moreover, there is uncertainty as to which LMWH preparations should be used for bridging for which indication. For instance, for bridging patients with mechanical heart valves there are only few bridging studies done with enoxaparin,^{18,19} while in practice all kinds of LMWH preparations are used. One way to reduce uncertainty might be to monitor LMWH activity around surgery, by anti-Xa activity measurements. Optimal anti-Xa levels are unknown for this indication, hence, laboratory based optimization is in fact impossible. Overall, one should conclude that after all, there is no firm basis for the use of LMWH bridging regimens, given the poor efficacy-benefit risk ratio and remarkable uncertainty about type and dose of LMWH preparation. The fact that the administration is simple, allowing ambulant administration of s.c. injections, is no sufficient argument for LMWH bridging. Thus, the application of LMWH bridging, if still warranted, such as in patients with mechanical heart valves undergoing surgery, should be carefully re-considered.

Unfortunately and probably also driven by ease of treatment, we found that guideline adherence to bridging therapy is not optimal in a study investigating guideline adherence performed in the Netherlands.²⁰ In fact, in about half of patients, LMWH bridging was not indicated and these data are in line with other studies.^{21,22} We were unable to find an association of the observed aggressive treatment with anticoagulants and the high bleeding rates, possibly due a lack of contrast in our population; in some studies post procedural therapeutic doses of LMWH were identified as a risk factor for bleeding.^{23,24} Possibly due to the fact that the majority of the participants were outpatients, the period of exposure to LMWH was much longer than necessary according to the ACCP guidelines; in outpatients rigidly performed INR testing is often not feasible.²⁵ Overall TE incidence was low and in concordance with some other studies.^{24,26-28}

In our patient series we also studied the effects of surgery on the different procoagulant mechanisms. Surgery quickly induced a marked increment in thrombin generation (TG) peak and endogenous thrombin potential (ETP) values. In a further analysis of coagulation proteins we observed that in particular FXI had significant

effects on the rate and height of TG. This effect of FXI may support the apparent importance of this protein in driving the risk of postoperative thromboembolism, as illustrated by a recent trial showing better efficacy of FXI inhibition as compared to LMWH.²⁹ The rise in FVIII and fibrinogen occurs gradually. Several studies report increased levels of F VIII and fibrinogen until 2 days to 72 hours postoperatively.^{30,31} This may in part explain the protracted risk of thrombosis following surgery. Another contributor to the thrombosis risk may be the effect of reduced sensitivity to activated protein C (APC resistance). Likely though, the level of procoagulant changes will depend on the actual surgical stress inflicted and this may explain why, in spite of the exposure to these 3 prothrombotic effects during bridging therapy, this does not immediately result in a clinically evident prothrombotic situation. In the BRIDGE trial, the vast majority of patients underwent low risk for thrombosis procedures such that the indication for bridging may have been quite low to begin with. The lesson from this study may be that the indications for bridging, as we already postulated in the above, should be revised, while for truly high risk for thrombosis patients, the question of the optimal drug and dose should also be re-established.

Methodological issues

The main limitation of our systematic literature review is the fact that most included studies are of poor methodological quality; the majority of studies have single-armed, retrospective, observational designs. Furthermore, due to different patient groups and interventions most of the meta-analyses yielded heterogeneous results; hence only 1 pooled risk estimate could be presented. Our study investigating guideline adherence had a small sample size and data were analyzed retrospectively. We were unable to compare different institutions with respect to guideline adherence, so only a local view on bridging practices could be provided. The strength of this study is the well-defined study population that allowed us to establish guideline adherence. Results of the exploratory study into biochemical mechanisms during bridging episodes was not sufficiently powered to detect possible associations between different assays and bleeding and TE.

Clinical implications

Bridging is associated with an increased risk of bleeding, possibly caused by residual anti-Xa effects on the day of the intervention. The prescribing physician should closely monitor the patient's renal function during treatment and warrant a sufficiently long interval between the last pre-operative dose of LMWH and surgery. Frequent INR checks after VKA resumption, to minimize the period in which the patient is exposed

to both the anticoagulant effect of LMWH and VKA, might result in a decrease in postoperative bleeding risk. Physicians should be aware of the potential risks caused by over-treatment with anticoagulants during the peri-procedural period. The role of bridging anticoagulation in prevention of TE remains unclear, although several prothrombotic mechanisms caused both by the intervention and bridging seem to play a role. When the decision to apply bridging is taken, apart from exclusively weighing the risk of thromboembolism caused by patient's characteristics, as advocated by all guidelines (for instance high CHADS₂ scores in combination with atrial fibrillation), the risk of thromboembolism caused by surgery should be weighed also. More invasive surgery causes an elevated post-operative TE risk, therefore LMWH bridging might still be indicated.

In the near future more often patients will be orally anticoagulated with non-vitamin K oral anticoagulants (NOAC). In case of interruption for surgery, bridging with LMWH should not be indicated in such patients. However, also in these patients, timing between cessation of NOAC and surgery is not self-evident. Particularly in elderly subjects with varying renal function, the apparent half-life of NOACs may be altered such that significant accumulation of NOAC activity occurs.^{32,33} In such cases clinically relevant bleeding risks may occur and routine check of renal (and liver) function prior to surgery is definitely warranted. In addition, the use of activity measurements like TG for NOACs may be considered, at least in patients with declining renal function.

Future implications

Sufficiently powered studies into the effects of bridging therapy on the incidence of perioperative TE should further clarify the role bridging therapy plays in combination with the prothrombotic effect of surgery in the onset of TE. Further study of the interaction of LMWH, VKA and surgery on the incidence of bleeding and TE is an important next step towards a better understanding of the mechanisms involved in bridging therapy. The possible role of the TG assay in assessing the pro or anticoagulant status of patients undergoing bridging can be explored in further studies. These future initiatives might result in more solid evidence with regard to bridging and even might result in a personalized bridging advice.

Venous stenting and antithrombotic therapy

Findings in perspective

The main conclusions of our systematic review on venous stenting and antithrombotic therapy are:³⁴ 1) post procedural antithrombotic therapy is not assessed separately as a potential factor for short-term and long-term failure or success of the stenting procedure in any of the presented studies, 2) most stented patients receive warfarin only for the standard duration of the treatment of their underlying DVT. This practice is in accordance with current ACCP guidelines.³⁵ In only 4 studies patients received additional antiplatelet therapy after stent placement.³⁶⁻³⁹ Anticoagulants likely play a more important role than antiplatelet agents in the prevention of re-stenosis in venous stented patients with a prior DVT;^{35,40} in-stent thrombosis is primarily caused by increased thrombin generation.⁴¹

We identified TTR as the most important predictive variable that reflects the quality of anticoagulant therapy and its associated risk for in-stent thrombosis. A 10% increase in TTR resulted in a risk reduction for in-stent thrombosis of 46.1%. In case of in-stent thrombosis also the proportion of INR values <2.0 are expected to be of interest. And although not significant, an increase of 10% in proportion of INR values <2.0 was associated with an 18.4% increase in in-stent thrombosis. The reason for this lack of significance may be due to the relatively small sample size and the lack of contrast in the population. LMWH was prescribed for INR <2.5 in both patients without in-stent thrombosis and patients with a thrombotic event in equal proportions, which may have further obscured possible differences. Besides the association between TTR and sub therapeutic INR values, another phenomenon with regard to TTR and in-stent thrombosis might play a role. Patients with low TTR experience more periods of increasing/decreasing effects of VKA; during periods of increasing effects the relatively low concentrations of active anticoagulants protein C and protein S compared to high concentrations of active procoagulant proteins FX and prothrombin might induce a prothrombotic state irrespective of the INR value.

In addition, the overall percentage of INR values <2.0 was low in this population, compared to other studies;⁴²⁻⁴⁴ 45.6% of patients had an INR target range of 3-4. Compared to other studies low rates of TTR were found. This can be explained at least partially by the fact that the study population consists of patients with a relatively short period in which TTR was calculated. In patients with shorter follow-up lower TTR values were recorded; (re)initiation after surgery of VKA therapy leads to unstable INR values during the first 6 weeks and results in a lower TTR.⁴⁵ A very limited number of the patients in our study switched from VKA to rivaroxaban, a direct FXa inhibitor.

Therefore, no comparison in terms of in-stent thrombosis between rivaroxaban and VKA could be made. Rivaroxaban has a more stable anticoagulant effect compared to VKA, caused by the fact that rivaroxaban shows less interactions with concomitant drug use, genetic factors and food intake.⁴⁶ Possibly, rivaroxaban or other NOACs might have a better efficacy profile than VKA in patients with iliofemoral stents, but this requires new studies on this matter. The strong effect of TTR on in-stent thrombosis is an indication that further improvement of anticoagulant therapy in stented patients should at least be aimed for.

Methodological issues

A major limitation of the systematic review is the fact that no meta-analysis could be performed. Applicability of the review may be affected by the fact that most studies assessed patient groups undergoing catheter directed thrombolysis (CDT) and/or percutaneous mechanical thrombectomy (PMT) of which only a part underwent stenting; subgroups consisting of only stented patients could be assessed in only a few cases. Our study into the effect of quality of anticoagulant therapy had a small sample size. This can be explained by the fact that venous stenting is a relatively new treatment modality, not performed on a large scale. The strengths of this study are: clear definition of endpoints, objectively documented recurrence, and regular follow up of the patients.

Clinical implications

With increasing application of venous stents in patients that require anticoagulant treatment for DVT, the management of anticoagulation will deserve more consideration. Our data suggest that the quality of anticoagulant management is perhaps an even more important determinant of the risk of re-thrombosis than in patients without stents. So far, most patients with venous stents are treated with VKA, sometimes antiplatelet drugs are added to further reduce the risk of stent occlusion. The quality of VKA therapy is an important tool to avoid patency failure, and must be optimized by frequent monitoring, advice on dietary intake and emphasis of the importance of adherence. Based on results presented in different studies it is not possible to give an indication of optimal INR target range; in our study the INR target range did not influence the risk of in-stent thrombosis, therefore an INR target range of 2.0-3.0 is possibly optimal, since this range minimizes the bleeding risk. The optimal duration of anticoagulant treatment is hard to pinpoint as no time dependent effects were observed in our study.

Future implications

Future studies in which the optimal length and intensity of VKA therapy is studied may help to further improve VKA management in patients with venous stents. A comparison of conventional VKA therapy, stratified according to TTR ranges and NOAC in terms of in-stent thrombosis might also be needed to expand the range of antithrombotic options in these patients.

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Samenvatting

Studies naar veiligheidsaspecten van verschillende antistollingsbehandelingen

Bij de behandeling van patiënten met antistollingsmiddelen zoals laag molecuulair-gewicht heparine (LMWH) en/of vitamine K antagonisten (VKA) dient te allen tijde een afweging gemaakt te worden tussen het risico op een trombo-embolie (TE) en het risico op een bloeding (mede) ten gevolge van de behandeling met deze preparaten. De balans tussen deze risico's wordt onder andere bepaald door de karakteristieken van de patiënt, de aard en ernst van de aandoening waarvoor antistolling wordt gegeven en of er een ingreep gaat plaatsvinden. In richtlijnen is getracht het beschikbare bewijs samen te vatten tot bruikbare richtsnoeren voor de behandeling van patiënten.

Het eerste deel van dit proefschrift behandelt de invoer en evaluatie van een clinical decision system (CDS) dat een gepersonaliseerd behandeladvies met LMWH ter voorkoming van veneuze trombo-embolie (VTE) genereert voor patiënten die op een afdeling interne geneeskunde opgenomen zijn. Eerdere studies wijzen uit dat deze patiënten vaak geen profylaxe ontvangen terwijl de indicatie hiervoor wel aanwezig is. Uit onderzoek blijkt eveneens dat de juiste toepassing van CDS de incidentie van diep veneuze trombose en longembolieën kan doen afnemen. In **Hoofdstuk 2** wordt deze studie beschreven. Een in het elektronisch patiëntendossier geïntegreerde risicoscore werd gebruikt om het risico op een veneuze trombo-embolie (VTE) en het bloedingsrisico te schatten. We concluderen dat er geen verbetering heeft plaatsgevonden in de naleving van richtlijnen met betrekking tot tromboseprofylaxe na introductie van CDS; er was een niet-significante toename van overbehandeling met LMWH waarneembaar. Mogelijke verklaringen voor deze resultaten zijn suboptimaal gebruik van CDS, afwijking van CDS ten gevolge van voorkeuren van de patiënt en een verhoogde waakzaamheid voor VTE risico door invoering CDS.

Het tweede deel van dit proefschrift behandelt overbruggingstherapie: de vervanging van VKA door LMWH in de periode rondom een operatie. Richtlijnen voor deze aanpak worden niet gedragen door veel bewijs; mede om deze reden presenteren we in **hoofdstuk 3** de resultaten van een 'systematic review' van de beschikbare literatuur over dit onderwerp. Overbruggingstherapie wordt vergeleken met de perioperatieve continuering van VKA en met het perioperatief stoppen van VKA. We hebben als uitkomsten postoperatieve bloeding en TE gedefinieerd. Op grond van de resultaten van deze review valt geen conclusie te trekken over het effect van overbrugging op TE, vergeleken met de overige 2 behandelopties; de incidentie van TE

is in alle studies laag. Uit een meta-analyse uitgevoerd met behulp van studies waarin patiënten pacemaker/implanteerbare defibrillator chirurgie ondergingen bleek overbruggingstherapie vergeleken met VKA continuering een verhoogd risico op postoperatieve bloedingen te veroorzaken.

In **hoofdstuk 4** wordt beoordeeld in hoeverre de richtlijnen voor overbruggings-therapie zoals die zijn uitgegeven door het American College of Chest Physicians (ACCP) zijn gevolgd bij patiënten die zijn overbrugd met LMWH en zijn opgenomen in het Maastricht University Medical Center (MUMC+); daarnaast hebben we mogelijke risicofactoren voor bloedingen vastgesteld. Overbruggingsrichtlijnen werden slecht opgevolgd, wat leidde tot langdurige behandelingen, overbehandeling en een hoge incidentie van bloedingen. De meerderheid van de patiënten had een laag TE risicoprofiel en onderging ingrepen met een laag risico op bloedingen. We hebben, in tegenstelling tot andere auteurs, in deze studie geen verband kunnen leggen tussen deze agressieve behandeling en het veelvuldig optreden van bloedingen. De lage incidentie van TE is in overeenstemming met andere studies. Bij patiënten met een verminderde creatinineklaring dienen verlaagde doses LMWH overwogen te worden, ten einde het bloedingsrisico te minimaliseren.

In **hoofdstuk 5** hebben we de effecten van overbruggingstherapie beoordeeld aan de hand van verschillende laboratoriumbepalingen, waaronder INR, anti-Xa, concentraties van verschillende stollingsfactoren en trombinegeneratie (TG). Een aantal patiënten werd gedurende de gehele overbruggingsperiode van negen dagen gevolgd door middel van dagelijkse bloedafnames tijdens een pilot studie. Ondanks residuele anti-Xa effecten is er een opmerkelijke verhoging van TG vastgesteld in relatie tot de ingreep. Perioperatief treden er drie pro-trombotische effecten op: FXI afhankelijke TG, afgenomen activiteit van de geactiveerde proteïne C route en de postoperatieve toename van acuut fase eiwitten FVIII en fibrinogeen. Verder onderzoek is noodzakelijk om de rol van verschillende assays tijdens de overbruggingsperiode vast te stellen.

De laatste twee decennia heeft het plaatsen van veneuze stents na een diep veneuze trombose (DVT) meer aandacht gekregen. Het laatste deel van het proefschrift behandelt antistolling na veneuze stenting. Het merendeel van de studies dat de veiligheid en effectiviteit van deze ingreep evalueert is van matige methodologische kwaliteit. In **hoofdstuk 6** worden de resultaten van een 'systematic review' gepresenteerd. In deze review wordt getracht de beschikbare literatuur over veneuze stentplaatsing en antitrombotische therapie te ordenen. Antitrombotische therapie

lijkt op basis van de beschikbare literatuur geen van de uitkomsten (terugkerende DVT, doorgankelijkheid van de stent, post trombotisch syndroom of bloedingen) te beïnvloeden. Dit kan worden verklaard omdat tot op heden is de associatie tussen de kwaliteit van antistollingstherapie met VKA, uitgedrukt als de proportie van de tijd die de patiënt zich in de juiste therapeutische range (TTR) bevindt en de effectiviteit van stentplaatsing nog niet expliciet is bestudeerd. In **hoofdstuk 7** wordt de relatie tussen kwaliteit van antistolling en in-stent trombose onderzocht. We concluderen dat een verhoging van de TTR bescherming biedt tegen in-stent trombose. De proportie van INR waarden <2.0 komt uit de analyses niet als risicofactor voor in-stent trombose.

Valorisatie

In westerse landen wordt op grote schaal, in het bijzonder bij ouderen, gebruik gemaakt van antistollingsmiddelen zoals vitamine K antagonisten (VKA) en laag molecuulgewicht heparine (LMWH). Indicaties voor het gebruik van deze middelen zijn onder meer atrium fibrilleren, kunstmatige hartklep, diep veneuze trombose (DVT) (therapeutisch en profylactisch), veneuze stentplaatsing en overbrugging bij ingrepen. De effectiviteits- en veiligheidsaspecten van behandeling met VKA en/of LMWH betreffen hoofdzakelijk het risico op bloedingen en trombo-embolieën (TE) ten gevolge van de behandeling met deze middelen en de aandoening waarvoor de antistolling wordt voorgeschreven. Er zijn in dit proefschrift drie onderwerpen behandeld.

Het eerste deel (Hoofdstuk 2) behandelt de introductie en de evaluatie van het introduceren van een clinical decision support (CDS) waarbij een geautomatiseerd en gepersonaliseerd behandeladvies met LMWH ter voorkoming van veneuze trombo-embolie (VTE) wordt gegenereerd. Studies tonen aan dat een belangrijk deel van de patiëntenpopulatie met een indicatie voor profylactisch LMWH gebruik dit niet ontvangt; dit geldt in het bijzonder voor niet chirurgische patiënten.(1) Eerdere, op verschillende locaties ingevoerde CDS systemen leidden tot een afname van de incidentie van DVT.(2) De relevantie van de door ons uitgevoerde evaluatie van CDS in het Maastricht University Medical Center (MUMC+), is gelegen in de constatering dat er aan een succesvolle invoering van CDS een aantal voorwaarden zijn gekoppeld waaraan moet worden voldaan. De belangrijkste voorwaarden zijn: minimale tijdsinvestering door voorschrijvend artsen, goede voorlichting aan gebruikers over de mogelijke positieve effecten van CDS in termen van VTE incidentie en de wetenschappelijke basis van het gegenereerde advies. Hiernaast lijkt het van groot belang dat de invoer ‘breed wordt gedragen’ door zowel directie, ICT-diensten als artsen. Deze constatering kan beleidsmakers en artsen die betrokken zijn bij de totstandkoming van toekomstige CDS projecten helpen de kans op een effectief CDS te vergroten. De investering in CDS kan eenvoudig worden terugverdiend doordat minder kosten hoeven te worden gemaakt voor de behandeling van DVT en longembolieën. Longembolieën leiden niet zelden tot het overlijden van de patiënt, terwijl DVT kan leiden tot levenslange beperkingen bij de patiënt.

Deel twee van dit proefschrift (Hoofdstuk 3-5) behandelt overbruggingstherapie: de vervanging van VKA door LMWH in de periode rondom een operatie. Deze aanpak wordt wereldwijd toegepast. Richtlijnen voor deze aanpak worden niet gedragen door uitvoerig bewijs.(3) De huidige, in richtlijnen aanbevolen manier om overbruggingstherapie uit te voeren leidt tot een verhoogd bloedingsrisico, terwijl het

TE risico onduidelijk blijft.(4) Monitoring van de hemostase bij de overbrugging van antistolling bestaat uit het uitvoeren van INR bepalingen. Als de INR zich op de dag van de ingreep rond de 1 bevindt, kan de ingreep doorgang vinden; als na de ingreep de INR twee opeenvolgende dagen 2.0 of hoger is kan er worden gestopt met LMWH toediening. Uit de in dit proefschrift gepresenteerde resultaten blijkt dat deze aanpak wellicht tekort schiet; een mogelijke rol voor anti-Xa bepalingen in verband met residuele antistolling ten tijde van de ingreep, in het bijzonder bij patiënten met een verminderde nierfunctie en bij patiënten die een therapeutische behandeling met LMWH ondergaan verdient zeker aandacht in verdere studies. Het gebruik van nieuwe technieken zoals de ook door ons onderzochte trombinegeneratie kan daarbij overwogen worden. Voorschrijvend artsen en trombosediensten verantwoordelijk voor de patiëntveiligheid kunnen op deze wijze het aantal postoperatieve bloedingen tijdens overbruggingsepisoden wellicht verder beperken. De door ons uitgevoerde studies kunnen een opmaat vormen voor verandering in de wijze waarop overbrugging wordt gemonitord en wellicht ook leiden tot een meer op maat afgestemde behandeling met LMWH. Een aanpassing van overbruggingsprotocollen en bevordering van bewustwording bij artsen dat bloedingsrisico's wellicht op grote schaal worden onderschat vormen een direct doel van dit proefschrift. Belangrijk is dat toekomstige onderzoekers aanvullend bewijs genereren voor de relevantie van een gewijzigde benadering van het fenomeen overbruggingstherapie.

Het laatste deel van dit proefschrift (Hoofdstuk 6 en 7) behandelt antistolling na veneuze stenting. In tot dusver gepubliceerde studies lijkt antitrombotische therapie geen van de uitkomsten (terugkerende DVT, doorgankelijkheid van de stent, post trombotisch syndroom of bloedingen) te beïnvloeden. Onze studie toont echter aan dat het risico op in-stenttrombose mede bepaald wordt door de kwaliteit van antistolling, weergegeven als de tijd binnen de therapeutische range. Artsen moeten doordrongen worden van het belang van kwaliteit van antistolling na plaatsing van een veneuze stent; dit kan betekenen dat een strikte monitoring van de INR belangrijker is dan tot dusver werd aangenomen. Wellicht is hier adequate antistolling met LMWH direct na insertie van de stent tijdelijk aangewezen. Toekomstige studies kunnen zich ook richten op de effecten van de nieuwe generatie antistollingsmiddelen, zowel de directe factor Xa als IIa remmers, die dankzij een naar verhouding stabiele farmacokinetiek wellicht sneller een stabiel niveau van antistolling kunnen realiseren. Een punt van overweging is evenwel of de vaste doseringen van deze directe remmers adequaat zijn voor alle patiënten die een veneuze stent krijgen. Specifiek onderzoek naar deze aspecten lijkt noodzakelijk.

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List of publications

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Dankwoord

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Curriculum vitae

About the author

Pieter Eijgenraam was born on October 27 1963 in Leiden, the Netherlands and finished his pre-university education at the Sint Maartenscollege in Maastricht in 1984. From 1984 to 1987 he studied Dutch law at the Maastricht University (Propaedeuse 1985) and the University of Nijmegen. From 1987 to 1995 he performed several jobs. In 1995 he started the Nurse education at the Maasland ziekenhuis in Sittard and was employed in this institution until 2000. In 2000 he accepted a job as a teacher at Gilde Opleidingen in Sittard. In 2002 he finished his teacher-training course at Hogeschool Arnhem Nijmegen (HAN). In 2008 he started the master program Epidemiology at Maastricht University. His internship was carried out in Department of Epidemiology where he wrote his thesis entitled: Medical conditions (diabetes mellitus type II, peptic ulcer, hepatitis, hypertension) and pancreatic cancer. Data from the Netherlands Cohort Study (NLCS) were analyzed. The results of this thesis were published in the British Journal of Cancer (BJC). In 2011 he started a part-time PhD project at the Laboratory for Clinical Thrombosis and Haemostasis of Maastricht University, Cardiovascular Centre MUMC+. The studies performed within this project resulted in the current thesis.