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Dissertation

**Bleeding complications in outpatients treated
with anticoagulation for venous
thromboembolism: clinical relevance of the
HAS-BLED bleeding score**

submitted by

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Graz, July 2017

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Declaration

“I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz”.

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Graz, July 2017

Disclosures

The current doctoral thesis was the basis for the preparation of a manuscript, which has been published in the journal “Seminars in Thrombosis and Hemostasis”. The published manuscript was drafted by the doctoral candidate, Peter Rief. Therefore significant parts of the doctoral thesis are similar to the published manuscript (with permission of “Seminars in Thrombosis and Hemostasis” editor-in-chief Emmanuel Falavro).

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Title:

Calculation of HAS-BLED Score is useful for early identification of VTE patients at high risk for major bleeding events – A prospective outpatients cohort study

All co-authors have explicitly agreed to the use of their data in the thesis.

The author of the dissertation hereby confirms that he has permission to reproduce the tables used in this work. If necessary, these were provided with the corresponding references.

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Abbreviations

PE: pulmonary embolism

DVT: deep vein thrombosis

SVT: superficial vein thrombosis

VTE: venous thromboembolism

rtPA: recombinant tissue plasminogen activator

ULN: upper limit of normal

PTS: post thrombotic syndrome

CTEPH: chronic thromboembolic pulmonary hypertension

GSV: great saphenous vein

AT: antithrombin

Tc: Technetium

CT: computed tomography

e.g.: exempli gratia (for example)

ACCP: American college of chest physicians

VKA: vitamin K antagonist

NOAC: non-vitamin K oral anticoagulant

LMWH: low molecular weight heparin

UFH: unfractionated heparin

aPTT: activated partial thromboplastin time

HIT: heparin induced thrombocytopenia

INR: international normalized ratio

APL: antiphospholipid syndrome

CI: confidence interval

AF: atrial fibrillation

mg/dl: milligram per deciliter

micromole/L: micromole per Liter

NSAIDs: nonsteroidal anti-inflammatory drugs

i.e.: id est (that is)

mL/min: milliliter per minute

OR: odds ratio

BMI: body mass index

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Zusammenfassung

Ziele: Die Hemmung des plasmatischen Gerinnungssystems ist die Therapie der Wahl nach stattgehabter venöser Thromboembolie (VTE). Ziel ist die Verhinderung eines VTE-Rezidivs. Die Antikoagulation birgt jedoch das Risiko klinisch relevanter Blutungen. Ziel der Studie war die prospektive Evaluierung der Vorhersagekraft von Blutungskomplikationen durch den HAS-BLED Score für VTE Patienten unter Langzeit-Antikoagulation. Die in der Studie untersuchten Patienten wurden mit unterschiedlichen Antikoagulantien behandelt.

Methoden: Es wurden die Daten von 111 Patienten, die an der Ambulanz der Angiologie des LKH Graz betreut wurden, prospektiv analysiert. Abhängig von der blutgerinnungshemmenden Medikation wurden die Patienten in 3 Gruppen unterteilt. Der HAS-BLED Score und die Dokumentation von weiteren Risikofaktoren und stattgehabten Blutungen wurden bei Einschluss in die Studie und danach 6-monatlich für 1 Jahr erhoben.

Ergebnisse: Patienten mit einem HAS-BLED Score ≥ 3 hatten ein signifikant erhöhtes Risiko für relevante Blutungskomplikationen (definiert als tödliche Blutung; Blutung mit einem Abfall des Hämoglobin um >20 g/L (1.24mmol/l) oder größer bzw. Notwendigkeit zur Substitution von zumindest 2 Erythrozytenkonzentraten; symptomatische Blutung in einem Organsystem oder kritischen Körperregion (z.B. intrakranial, retroperitoneal, intraspinal, intraokular, intraartikular, perikardial, intramuskulär mit Kompartmentsyndrom) (Odds Ratio (OR) 13.05, 95% Konfidenzintervall (CI): 0.96 - 692.58, $p = 0.028$) und tendenziell auch für schwächer ausgeprägte Blutungen (OR 2.25, 95%CI: 0.87 - 5.85, $p = 0.091$) im Vergleich zu Patienten mit einem HAS-BLED Score < 3 .

Schlussfolgerung: Wir konnten zeigen, dass bei Patienten, die aufgrund einer VTE eine längerfristige Antikoagulation benötigen, ein HAS-BLED Score von ≥ 3 mit einem erhöhten Risiko für relevante Blutungskomplikationen einhergeht.

Abstract

Objectives:

The aim of this study was the prospective evaluation of the performance of the HAS-BLED score in predicting major bleeding complications in a real-world outpatient cohort, during long term anticoagulation for venous thromboembolism (VTE), treated with a broad spectrum of anticoagulants.

Methods:

We analyzed 111 outpatients objectively diagnosed with VTE and treated long term with various anticoagulants. Patients were grouped in three cohorts based on anticoagulant regimen. Calculation of the HAS-BLED score and documentation of bleeding events were performed every six months for one year.

Results:

Patients with a HAS-BLED score ≥ 3 had an increased risk for major bleeding events (odds ratio (OR) 13.05, 95% confidence interval (CI): 0.96 - 692.58, $p = 0.028$) and a trend to higher risk for minor bleeding events as well (OR 2.25, 95%CI: 0.87 - 5.85, $p = 0.091$) when compared to patients with a HAS-BLED score < 3 .

Conclusion:

This indicates that a HAS-BLED Score ≥ 3 allows for identification of VTE-patients on long-term anticoagulation at increased risk for major bleeding, regardless of the anticoagulant agent used.

1 Introduction

Overview over Venous Thromboembolism

1.1 Definition

The term venous thromboembolism (VTE) implicates deep vein thrombosis (DVT) and pulmonary embolism (PE). (1)

In case of clot formation in a subfascial vein, a partial or total obstruction of the affected vein occurs. This entity is called DVT. If parts of the thrombus migrate with the blood to a lung artery a so called PE occurs.

VTE is a frequent and potentially fatal disease with multifactorial etiology and often consequences long-term complications such as post-thrombotic syndrome (PTS) (2) and chronic thromboembolic pulmonary hypertension (CTPH). (3)

Anticoagulant treatment is the recommended standard therapeutic approach for VTE patients to reduce the risk of related cardiovascular death and the risk of recurrent VTE as well. (1)

1.2 Terminology in VTE

“Unprovoked”: No preceding risk factor for VTE is evident.

“Provoked”: VTE related to e.g. pregnancy, cancer within the last 6 weeks to 3 month before diagnosis. (4)

The European Society of Cardiology (ESC) (1) recommends the pulmonary embolism severity index (PESI) (5) to classify acute PE in “high risk” and “low risk”. The parameters age >80 years, cancer, chronic heart failure, hypotension (<100mmHg systolic blood pressure), tachycardia (>110 beats/minute) and arterial oxyhemoglobin saturation <90% form the simplified version of the PESI score. By adding up 1 point for each parameter present in a patient with acute PE allows to

estimate the 30-day mortality risk. Low risk (0 points) and high risk (≥ 1 point) has a reported 30-days mortality of 1% and 10.9% respectively. (5)

1.3 Epidemiology

VTE is the third most frequent cardiovascular disease with an estimated average annual incidence rate of 100–200 per 100 000 inhabitants and it is mainly a disease of older age. (6) Men got a higher incidence rate (130 per 100 000) than women (110 per 100 000). (7) In contrast the reported annual incidence of VTE in children (1.4 – 57 per 100 000) is much lower compared to those of adults. (8,9)

About 25 to 40% VTE events are classified as spontaneous. (10) Existing data on VTE recurrence suggest that especially in spontaneous VTE events it is a chronic disease with periodic return. About one third of VTE patients develop a second event within the next 10 years. (11,12) The risk of VTE-recurrence is highest within the first 6-12 months after the initial event. Afterwards it is getting lower but it never disappears. (13) In about 25% sudden death is the initial clinical presentation of patients with PE, further the overall survival after PE is much worse than after DVT alone. (14)

1.4 Etiology

Rudolf Virchow was the first to describe the pathogenesis of thrombosis.

The Virchow's triad summarizes three conditions substantially involved in the development of thrombosis (15):

- Hypercoagulability
- Stasis
- Endothelial dysfunction (by injury) (15)

A change of any of these components is able to trigger a thrombotic event. The aberrations can be categorized as hereditary or acquired.

1.5 Risk factors

Wells et al. (16) summarized these risk factors for VTE as follows:

“Hereditary risk factors associated to hypercoagulability:

- Factor V Leiden Mutation
- Prothrombin G20210A Mutation
- Deficiencies in Antithrombin (AT), Protein S and C, Plasminogen
- Antiphospholipid Antibody Syndrome

Acquired risk factors associated to hypercoagulability:

- Cancer
- Chemotherapy
- Oral contraceptives and hormone replacement therapy
- Pregnancy and post-partum period
- Central obesity
- Heparin-induced thrombocytopenia

Risk factors associated to stasis:

- Reduced mobility
- Polycythemia
- Endothelial injury
- Congestive heart failure

Risk factors associated to endothelial dysfunction:

- Endothelial damage through arterial hypertension or cigarette smoking, trauma, surgery, venous catheters

Risk factors with mixed entity:

- Older age

- Previous VTE,
- Inflammatory and autoimmune diseases,
- Nephrotic syndrome,
- Low levels of protein S,
- High factor VIII, or IX, or XI
- Elevated Fibrinogen levels” (16)

Approximately half of the VTE events diagnosed are classified as provoked. This means that a triggering factor(s) is (are) known. The other half is unprovoked (idiopathic or spontaneous), meaning that the reason is not known so far. (17-19)

Initial studies exploring the natural history of VTE were performed after orthopedic surgery during the 1960s. The findings showed that patients were at highest risk of VTE during the first three months after surgery and a significant reduction of that risk could be achieved by administering antithrombotic prophylaxis. (20)

1.6 Pathophysiology

Underlying pathogenic mechanisms are only partially known, but it is widely accepted that the combination of hypercoagulability and stasis is determining for the occurrence of VTE, more than endothelial damage. This is because a venous thrombus is predominantly built up of erythrocytes and fibrin, and to a lower degree of platelets. (21)

Acute PE decreases the blood flow and therefore the oxygenation of blood within the lungs. Right ventricular heart failure as a consequence of diminished circulation is supposed to be the pathomechanism of fatal PE. Thirty to fifty percent obstruction by thrombus material is postulated to be the limit leading to increased pulmonary artery pressure. (22) Further, PE induces the release of vasoactive (vasoconstrictive) substances such as serotonin and thromboxane A₂. (23) The combination of these two entities is the reason that pulmonary vascular resistance escalates due to PE. (24)

Initially the right ventricular myocardium is able to raise the contractile properties via the Frank Starling mechanism. (25) But the right ventricle is thin-walled and therefore incapable to tolerate a pulmonary artery pressure beyond 40mmHg over a longer period of time. For that reason increased pulmonary vascular resistance results in right ventricular dilatation. Moreover, this dilatation leads to a shift of the interventricular septum and afterwards to a decreased left ventricular filling and therefore to a reduced cardiac output. (26)

1.7 Classification

1.7.1 Deep vein thrombosis:

DVT mostly affects the lower extremities. (27,28)

Depending on the affected location a differentiation into

distal deep vein thrombosis

- fibular
- posterior
- anterior tibial veins
- muscular veins

and proximal deep vein thrombosis

- popliteal
- femoral
- pelvic veins

is mandatory.

So far various other locations for venous thrombotic events were described. These are the hepatic-, renal-, portal-, ovarian-, mesenteric-, cerebral- and upper extremity veins.

1.7.2 Pulmonary embolism:

The pulmonary artery may be affected in the

- main
- segmental
- or sub segmental branches.

1.7.3 Superficial venous thrombosis (SVT):

In the literature so far the term SVT is used controversially. Thromboses in superficial veins include all superficial veins over the body. However clinically relevant are thrombotic events of the great saphenous vein (GSV) and the small saphenous vein.

1.8 Clinical Symptoms

The clinical presentation of DVT and PE is heterogeneous and non-specific:

The following symptoms are common in acute PE: (29)

- dyspnea
- pleuritic chest pain
- cough
- substernal chest pain
- fever
- hemoptysis
- syncope
- arterial hypotension and shock
- tachycardia

Common symptoms in DVT: (29)

- unilateral leg pain
- warmth
- edema
- erythema
- dilated superficial veins (collaterals) of the leg

1.9 **Assessment of clinical probability**

Because of limited specificity and sensitivity of clinical signs the pre-test probability needs to be evaluated. For this the Wells score as well as the Geneva score are standardized and validated and therefore the most frequently used tools. (30-32)

Table 1: Wells score and Revised Geneva Score (30-32)

Wells Score		Revised Geneva Score	
<u>Variable</u>	<u>Points</u>	<u>Variable</u>	<u>Points</u>
Previous DVT or PE	1.5	Age>65 years	1
Recent surgery or immobilization	1.5	Previous DVT or PE	3
Cancer	1	Surgery or fracture within 1-month	2
Hemoptysis	1	Active malignancy	2
Heart rate > 100 beats/min	1.5	Unilateral lower limb pain	3
Clinical signs of DVT	3	Hemoptysis	2
Alternative diagnosis less likely than PE	3	Heart rate 75-94 beats/min	3
		Heart rate >95 beats/min	5
		Pain on lower limb deep vein at palpation and unilateral edema	4
<u>Clinical probability (3 levels)</u>	<u>Total</u>	<u>Clinical probability (2 levels)</u>	<u>Total</u>
Low	0-1	Low	0-3
Intermediate	2-6	Intermediate	4-10
High	>7	High	>11
<u>Clinical probability (2 levels)</u>		<u>Clinical probability (2 levels)</u>	
PE unlikely	0-4	PE unlikely	0-3
PE likely	>4	PE likely	>3

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; min, minute. Reproduced from Wells et. al (30) with permission of publisher Wolters Kluwer Medknow Publications

1.10 Laboratory testing

Acute VTE causes elevated plasma D-dimer levels. However, elevated D-Dimer levels are unspecific for VTE as several reasons can cause elevated D-Dimer levels (e.g. recent surgery, inflammation, trauma, cancer etc.). (33)

A diagnostic sensitivity of 95% implicates a high negative predictive value so that a normal D-dimer level makes acute VTE unlikely. (34) In conclusion, D-dimer testing helps to rule out VTE in symptomatic patients with only low to moderate pre-test probability. (34)

1.11 Imaging

1.11.1. Ultrasound → Method of choice for imaging DVT.

Compression venous ultrasonography has replaced venography for diagnosis of DVT with a sensitivity >90% and a specificity of 95%. (35)

1.11.2. Computed tomographic (CT) pulmonary angiography → Method of choice for imaging PE.

Due to technical evolution in the last decades CT pulmonary angiography is the examination of choice for imaging of the pulmonary arteries. A sensitivity of over 80% and a specificity of over 95% were reported in the PIOPED II trial. (36)

1.11.3. Ventilation-perfusion scintigraphy

This examination is performed with technetium (Tc)-99m-labeled albumin particles as an established diagnostic test. A mismatch like a normal ventilation with a hypo perfused lung area (with an unremarkable chest X-ray) is considered as a sign for PE. The sensitivity and specificity is much worse than that of CT angiography and therefore this examination method might be used if CT angiography is not possible

for some reason (e.g. renal failure, contrast medium-induced anaphylactic reaction). (37)

1.11.4. Pulmonary angiography was widely displaced in the last decades by CT angiography offering equal diagnostic accuracy. (38) It's an invasive procedure with possible procedure-related complications (39) and therefore nowadays mostly used to guide catheter-directed treatment of acute PE.

1.11.5. Magnetic resonance angiography is not used routinely due to its low sensitivity in diagnosing PE. (40)

1.11.6. Echocardiographic examination can detect right ventricular overload and dysfunction potentially triggered by acute PE and is therefore an indirect diagnostic tool. In clinical practice echocardiographic findings are of importance for risk stratification of PE patients. (5)

So far guidelines recommend the current approach for the diagnosis of VTE as follows: (1,41-43)

“-Validated clinical prediction rules should be used to estimate pretest probability of venous thromboembolism, both deep venous thrombosis and pulmonary embolism, and for the basis of interpretation of subsequent tests.

- In appropriately selected patients with low pretest probability of DVT or pulmonary embolism, obtaining a high-sensitivity D-dimer is a reasonable option, and if negative, indicates a low likelihood of VTE.

- Ultrasound is recommended for patients with intermediate to high pretest probability of DVT in the lower extremities.

- Patients with intermediate or high pretest probability of pulmonary embolism require diagnostic imaging studies.”

1.12 Treatment

The current American College of Chest Physicians (ACCP) Guidelines define the aim of DVT-treatment as prevention of (43):

- pulmonary embolism
- post thrombotic syndrome
- recurrent venous thrombosis.

In terms of PE, the objective is the prevention of

- death by acute right ventricular heart failure and hypoxemia
- recurrent symptomatic PE.

As soon as VTE is confirmed, anticoagulant treatment is recommended immediately, except in case of existing contraindication. (43)

We nowadays know that especially in the first six to twelve months the risk of recurrent VTE is highest. However, although the annual recurrence rate drops, it remains elevated for many years. Following data on estimated cumulative percentages of VTE recurrence, published after a population-based cohort study of 1719 patients diagnosed with VTE (13), were:

- After 7 days (0.2 percent)
- 30 days (1 percent)
- 180 days (4 percent)
- 1 year (6 percent)
- and 10 years (18 percent).

Considering various etiologic causes for VTE as well as the required differentiation in first episode of VTE or recurrent VTE different guidelines for the duration of anticoagulant treatment exist.

1.12.1 Available anticoagulant agents

- Vitamin K Antagonists (VKA): Warfarin, Phenprocoumon, Acenocoumarol
- Factor Xa inhibitors: edoxaban, apixaban, rivaroxaban
- Direct thrombin inhibitor: dabigatran
- Low-molecular-weight heparin (e.g. dalteparin, fraxiparin, enoxaparin)
- Unfractionated heparin
- Pentasaccharide (Fondaparinux)
- Direct Thrombin Inhibitor (Argatroban)

1.12.2 Parenteral anticoagulation

Anticoagulant treatment with LMWH, unfractionated heparin (UFH) or fondaparinux is recommended as initial treatment of choice in patients presenting with VTE-symptoms, even if the results of diagnostic test are still under way. (1,43)

Unfractionated heparin (UFH): The advantages of UFH are a rather short half-life and its possible reversal by prothrombin sulfate. The heparin dosage is adjusted by measuring the activated partial thromboplastin time (aPTT). However, UFH has two major drawbacks compared to LMWH: higher risk of major bleeding as well as a higher risk for heparin-induced thrombocytopenia (HIT). (1,43)

LMWH: Licensed in Europe for the treatment of acute VTE are the following substances: Enoxaparin, Tinzaparin, Dalteparin, Nadroparin and Fondaparinux. As already mentioned above the risk of bleeding and HIT is lower compared to UFH and no routine laboratory monitoring is necessary, although the right dosage can be verified by measuring the anti-factor Xa activity 4 hours after the last injection. (1,43)

1.12.3 Oral anticoagulation

Vitamin K antagonists (VKA):

Before VKA are initiated UFH, LMWH, or fondaparinux should be administered for a minimum of 5 days. For decades VKAs have been the only oral treatment option for VTE patients. Warfarin, acenocoumarol, phenprocoumon, phenindione and flunidione are available substances. (44) INR monitoring is mandatory to find the correct dosage. A target INR level of 2.0-3.0 is recommended. (1,43)

Non-vitamin K oral anticoagulants (NOACs):

Three direct factor Xa inhibitors and one direct thrombin inhibitor are licensed for treatment of VTE nowadays. There were various reasons for the development of NOACs. These substances show at least the same efficacy in reducing recurrent VTE like VKA treatment. However, a significant reduction especially of intracranial bleeding and no need for laboratory testing are the main advantages of these substances compared to VKA.

Direct thrombin inhibitor:

Dabigatran was tested against warfarin in the phase III clinical trials RE-COVER and RE-COVER II. (45,46) In these studies Dabigatran was non-inferior to warfarin and fewer episodes of bleeding events were observed.

Direct factor Xa inhibitors:

Rivaroxaban was compared to enoxaparin/warfarin in the EINSTEIN-DVT and EINSTEIN-PE trials. (47,48) Non-inferiority was shown and moreover patients treated by rivaroxaban had lower rates of major bleeding events.

Apixaban revealed non-inferiority against conventional therapy (enoxaparin/warfarin) in the AMPLIFY study. (49) Similar to rivaroxaban major bleeding occurred less frequently in the apixaban group.

Edoxaban equally was compared to conventional therapy in a non-inferiority designed study, the Hokusai-VTE trial. (50) The result, recurrent symptomatic VTE

and/or fatal PE showed that edoxaban was non-inferior to VKA treatment. Furthermore bleeding episodes were less frequent.

1.12.4 Thrombolytic treatment

A systemic thrombolysis is recommended in patients with massive PE events classified as high-risk PE. This means that these patients are at a high mortality risk showing symptoms of hypotension and tachycardia (shock) defined in the guidelines of the European Society of Cardiology (ESC) as systolic blood pressure <90mmHg or drop of the systolic pressure by >40mmHg. (1) The aim in treating these patients is the early reperfusion of the pulmonary circulation. Based on the high risk of major bleeding complications in patients treated with systemic thrombolysis contraindications (e.g. neoplasm of the brain, surgery or trauma <2month, previous stroke <3month) have to be considered. Streptokinase, urokinase, and recombinant tissue plasminogen activator (rtPA) are licensed in Europe for this treatment. (1,43)

1.12.5 Surgical embolectomy

In case of contraindication present for thrombolysis or if thrombolysis was not successful, high risk PE patients (rarely in selected cases of intermediate-high-risk PE) should be evaluated for surgical embolectomy. (1,43) So far no randomized trials evaluated this procedure, however mortality rates are high. Therefore pulmonary embolectomy should be seen as a “last option” for patients with documented massive life threatening PE. (51)

1.12.6 Percutaneous catheter-directed treatment:

Possible interventional options in patients with intermediate and intermediate-high risk PE and contraindications to thrombolysis are:

- rotational thrombectomy
- mechanical comminution of thrombus (e.g. pigtail catheter)
- thrombus suction with aspiration catheters

The goal is to remove the obstructing thrombotic material to decrease the pulmonary artery pressure, relieve the right ventricle and improve the pulmonary gas exchange. If no contraindications to thrombolysis exist a catheter-directed (low-dose) ultrasound-accelerated thrombolysis can be performed. (1)

1.12.7 Recommendations for the selection of anticoagulant agent in VTE (ACCP-Guidelines) (43)

For VTE without cancer dabigatran, rivaroxaban, apixaban, edoxaban, vitamin K antagonist (VKA) and low-molecular-weight heparin (LMWH) therapy is suggested for long term anticoagulation, means at least 3 months. For VTE and cancer as an underlying disease LMWH is suggested over the oral anticoagulants VKA, Factor Xa inhibitors (apixaban, rivaroxaban and edoxaban) as well as dabigatran (Factor II Inhibitor). Recommended is that immediately after VTE-diagnosis treatment should be started with LMWH, fondaparinux or unfractionated heparin (UFH), rivaroxaban or apixaban. Afterwards further oral anticoagulation should be given. (43)

1.13 Duration of anticoagulation

Because the recurrence risk of VTE is different whether it is a first, recurrent, provoked or unprovoked VTE, different recommendations concerning the duration of anticoagulation exist.

1.13.1 Recommendations for the duration of anticoagulation in VTE

The ACCP-Guidelines (43) defined the following recommendations:

“First provoked proximal DVT and/or pulmonary embolism with transient risk factor:

→ Treatment with anticoagulation for 3 months

First provoked proximal DVT and/or PE with persistent risk factor

→ These patients are considered to have a higher than usual risk of recurrence. Indefinite anticoagulation in patients with persistent risk factors (e.g. malignancy, antiphospholipid antibody syndrome) must be decided on an individual basis

Recurrent provoked VTE

→ Treatment with anticoagulation for *at least* 3 to 6 months

First unprovoked VTE:

→ Extended anticoagulant treatment over 3 months of therapy

Recurrent unprovoked VTE

→ Recommended extended anticoagulant therapy (no scheduled stop date) over 3 months

VTE in cancer:

→ Rates of VTE recurrence are expected to be 15 percent or higher per year in active malignancy. So treatment with anticoagulation for at least 3 months is recommended. The risk varies considerably according to whether the cancer is active or cured, progressive or remission or metastatic. In these patients extended anticoagulation must be carefully reassessed in short time periods in respect of benefit over bleeding complication.” (43)

To summarize, usually the recommended shortest duration of anticoagulant therapy for DVT or PE is 3 months. ‘Extended anticoagulant treatment’ implies duration over 3 months usually continued indefinitely. (43)

1.13.2 Assessing the risk of recurrence

As already mentioned above, a minimum of 3 months duration of anticoagulation is recommended for patients with diagnosed VTE. To find out which patients benefit from a longer duration of anticoagulation, in a first step the recurrence risk of VTE needs to be assessed.

Kearon et al. published 2016 in the ‘American College of Chest Physicians Evidence-Based Clinical Practice Guidelines’ (43) following data:

- First episode of unprovoked VTE – 10 percent for the first year; 5 percent/year thereafter
- Second episode of unprovoked VTE – 15 percent for the first year; 7.5 percent/year thereafter
- First VTE provoked by surgery – 1 percent for the first year; 0.5 percent/year thereafter
- First VTE provoked by non-surgical factor – 5 percent for the first year; 2.5 percent/year thereafter

In all patients suffering from VTE an initial assessment for risk of recurrence based upon the clinical nature and background of the episode of VTE (e.g. provoked or unprovoked VTE, reversible or irreversible risk factors, first episode versus recurrent episode) should be done. Generally accepted is that VTE has the highest risk of recurrence in the first six months to one year following the initial event. This is also the rationale for anticoagulation for a minimum of three months. (43)

Existing long-term epidemiologic studies on patients with unprovoked VTE suggest a high lifetime recurrence risk of VTE which can be crucially reduced by a prolonged duration of anticoagulation beyond six months. (43)

This first step initial assessment may be further modified by the consideration of additional factors, which are predominantly important for those with a possible/unclear benefit from indefinite anticoagulation.

1.13.3 Assess additional risk factors for VTE recurrence

Second step: the decision to continue or stop indefinite anticoagulation needs to be done in considering of additional risk factors:

Persistent factors that increase the risk are:

- Active malignancy is a high risk factor for VTE. (52)

- Patients with antiphospholipid antibody syndrome (APL) are at increased risk of recurrent VTE. (53)

- Inherited thrombophilia

 - protein S deficiency (54), protein C and/or antithrombin III deficiency (55)

 - homozygous factor V Leiden mutation (56)

 - homozygous prothrombin gene mutations (57)

-Male gender is a frequently cited but controversial debated risk factor for recurrence following a first episode of VTE. (58)

-Hormonal – In a post hoc analysis of a randomized study (59) of low intensity warfarin, higher rates of recurrent VTE were reported when men were compared to women with hormonal-related thrombosis

-Older Age (60)

-Elevated D-dimer levels – A meta-analysis (61) of observational studies reported an elevated rate of VTE recurrence in patients with an elevated D-dimer (>500 ng/mL) at three to four weeks following termination of anticoagulation compared with patients with a D-Dimer level within normal range (9 to 17 percent versus 3 to 7 percent).

-Residual vein obstruction - Data are conflicting concerning the ability of residual vein obstruction predicting recurrence; however a 2011 systematic review of 11 randomized studies (2302 patients) reported that the presence of residual vein obstruction at the time of cessation of anticoagulation positively correlated with recurrent VTE, particularly in patients with malignancy. (62)

1.13.4 Patient values and preferences

It is very important that treating physicians discuss potential advantages and disadvantages of anticoagulant treatment given with the patients in detail. The patient's individual bleeding risk, recurrence risk, comorbidities and age should be discussed. (63)

1.14 Risk of bleeding

In a third and very important step, the individual bleeding risk needs to be assessed. The most feared complication of anticoagulant therapy is major bleeding. The definition of bleeding complications varies among different studies. Most of the studies (64-66) defined major bleeding as:

-fatal bleeding

-bleeding with a decrease in the hemoglobin level of 2 g per deciliter or more

-bleeding that required a blood transfusion of two or more units of blood

-bleeding into a critical site (intracranial, retroperitoneal, spinal, intraocular, intraarticular, pericardial or intramuscular with compartment syndrome)

Castellucci et al. (67) reported in a meta-analysis of 11 studies that included 3965 patients a major bleeding rate of 0.45 per 100 patient-years (95 % CI 0.29-0.64) and a fatal bleeding rate of 0.14 per 100 patient-years (95% CI 0.057-0.26).

Risk factors associated with bleeding during anticoagulant treatment are: (51,68)

- Age >65 years, doubled when Age >75 years
- Prior bleeding
- Cancer, doubled if metastatic or highly vascular
- High creatinine serum levels -> renal insufficiency
- Liver failure
- Diabetes
- Thrombocytopenia
- Prior stroke (above all if hemorrhagic)
- Anemia
- Concomitant antiplatelet or nonsteroidal anti-inflammatory therapy
- Recent surgery
- Frequent falls

- Alcohol abuse
- Reduced functional capacity
- Poor control of VKA therapy

The ACCP (43) estimated the rate of major bleeding as follows:

- Low risk (no risk factors present) – 1.6 percent during the first three months; 0.8 percent/year thereafter
- Intermediate risk (one risk factor present) – 3.2 percent during the first three months; 1.6 percent/year thereafter
- High risk (two or more risk factors) – 12.8 percent during the first three months; ≥ 6.5 percent/year thereafter

2 Bleeding scores

So far there are several validated bleeding scores for patients with atrial fibrillation (AF) on anticoagulant treatment. (69-72) However, concerning VTE so far no validated score is able to accurately predict major bleedings during anticoagulant treatment.

Overview

2.1.1 Bleeding scores to assess bleeding risk in VTE patients

So far 8 scores were published to predict bleeding complications in VTE patients on anticoagulant treatment:

- HAS BLED score (72)
- RIETE score (73)
- Kuijer score (74)
- Kearon score / ACCP scheme (43)
- OBRI score (75)
- VTE-BLEED score (76)
- EINSTEIN model (77)
- Hokusai model (78)

However, a simple applicability to use those predicting scores in clinical practice is a preferable precondition. The prediction models differ concerning the number of variables need to be evaluated to calculate the score. Specific reference is made to these scores in the discussion later on.

2.1.2 Further important bleeding scores to assess bleeding risk only in patients with atrial fibrillation

2.1.2.1 **ATRIA score**

This score was developed from the results of the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. (69) Variables included are:

- Anemia – 3 points
- Severe renal disease (estimated glomerular filtration rate <30 mL/min or patients on hemodialysis) – 3 points
- Age ≥75 years – 2 points
- Any prior hemorrhage – 1 point
- Diagnosed arterial hypertension – 1 point

Bleeding rates for low- (0 to 3 points), intermediate- (4 points), and high-risk patients (5 to 10 points) were 0.76, 2.62, and 5.76 events per 100 patient-years, respectively. (69)

2.1.2.2 **HEMORR2HAGES score**

The HEMORR2HAGES score (70) was created by combining risk factors from existing scoring systems. Each factor is assigned 1 point, only a previous bleeding episode takes 2 points):

- Hepatic or renal disease
- Ethanol abuse
- Malignancy
- Older age (>75 years)
- Reduced platelet count or function, including aspirin therapy
- Re-bleeding risk (history of prior bleed)
- Hypertension
- Anemia
- Genetic factors

- Excessive fall risk
- Stroke

Risks of major bleeding per 100 patient-years were 1.9% (0 points), 2.5% (1 point), 5.3% (2 points), 8.4% (3 points), 10.4% (4 points) and 12.3% (≥ 5 points). (70)

2.1.2.3 ORBIT score

Analyzing the records from the national Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry (79) pointed out 5 variables associated with bleeding:

- **O**lder age (>74 years) → 1 point
- **R**educed hemoglobin, hematocrit, anemia → 2 points
- **B**leeding history → 2 points
- **I**nsufficient kidney function (<60 mL/min/1.73 m²) → 1 point
- **T**reatment with antiplatelet agents → 1 point

Patients with a maximum of two points were graded low risk, three points medium risk and four or more points high risk. (79)

3 Study aim

Anticoagulation is recommended in patients with diagnosed acute venous thromboembolism (VTE). (1,43) The duration of treatment is at least three months, but especially in the case of idiopathic and recurrent VTE, long-term or indefinite anticoagulant treatment to prevent recurrent VTE, should be considered. (1)

Rates of anticoagulant-related major bleeding complications in patients with VTE are different when using vitamin K antagonist (VKA) or non-vitamin K oral anticoagulant (NOAC) therapy. A recent meta-analysis reported the risk of major bleeding during the first 6 months of treatment as being 1.1% and 1.8% among patients treated with NOAC or VKA respectively. Minor bleedings were estimated at 6.3% among NOAC and 8% among VKA recipients. (80)

The risk of bleeding complications due to anticoagulation indicates periodical re-assessment of the anticoagulant therapy. Several recent studies reported prediction models to classify the probability of bleeding events during anticoagulation. (73-75,81) However, so far no bleeding score with high predictive value for VTE patients has been published.

Only recently the 10th American College of Chest Physicians (ACCP) guidelines recommended the use of a bleeding score to decide whether patients with unprovoked VTE should be indefinitely treated with anticoagulants. (43) However, to the best of our knowledge, the bleeding score suggested in the ACCP guidelines was not evaluated prospectively elsewhere.

The HAS-BLED score was already validated in patients with atrial fibrillation (72,82,83) and therefore seemed to be the most useful score that examined bleeding risk in patients with VTE. (66,84)

The aim of our study was to prospectively evaluate the performance of the HAS-BLED score predicting bleeding complications in a real world outpatient cohort during long-term anticoagulation for VTE. (85) We further compared the HAS-BLED score with a recently published bleeding score for VTE patients (VTE-BLEED score). (76)

4 Methods

We prospectively observed 119 outpatients in our clinic (Medical University of Graz, Department of Angiology) who had been objectively diagnosed with VTE between October 2014 and November 2016. Of those, seven were not treated for VTE and were therefore excluded as screening failure. The aim was to analyze a “real-world” cohort of VTE patients. Therefore, the inclusion criterion to the study was ongoing anticoagulant treatment for diagnosed VTE, notwithstanding the prior duration of anticoagulation. Visits were conducted at 0, 6, and 12 months. Patients were grouped based on their anticoagulant medication (low molecular weight heparin [LMWH], NOAC, VKA), constituting three patient groups (Table 2). (85)

Table 2: Patients grouped based on their anticoagulant medication.

Number of patients	Anticoagulation	Substance
52	VKA	
40		Phenprocoumon
12		Acenocoumarol
20	LMWH	
13		Enoxaparin
8		Dalteparin
39	NOAC	
35		Rivaroxaban
2		Apixaban
2		Dabigatran

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The HAS-BLED score was calculated, we took blood samples and asked the patients about bleeding complications at each visit, at which point we reconsidered if further anticoagulation therapy was consistent with current guidelines. (85)

After blood was taken, the following laboratory parameters were evaluated: blood count, creatinine, blood urea nitrogen, liver transaminases (aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin), coagulation tests (prothrombin time, international normalized ratio [INR], activated partial thromboplastin time) and a lipid profile. The study protocol did not influence treatment decisions of the treating physician at any time. This was an observational trial and was approved by the ethics committee of the Medical University of Graz, Austria and all patients gave written informed consent. (85)

Major bleeding was defined as follows: fatal bleeding; bleeding with hemoglobin level reduction of >20 g/L (1.24mmol/l) or more, or need to transfuse two or more units of red blood cells; symptomatic bleeding in a critical area or organ (e.g. intracranial, retroperitoneal, intraspinal, intraocular, intraarticular, pericardial or intramuscular with compartment syndrome). (86)

All other bleeding complications (e.g. nosebleed, skin hematoma, gum bleeding, hemorrhoid bleeding) were graded as minor. (85)

4.1 Data collection

Complete data on demographic information (age and gender, body mass index [BMI], comorbid conditions (history of stroke and myocardial infarction, arterial hypertension, chronic liver and renal disease, cancer, anemia, drug abuse), concomitant medication (antiplatelet therapy, immunosuppressive medication) and laboratory findings were prospectively collected using standardized data collection forms.

The HAS-BLED score was assessed at baseline and at each of the two following visits. Referring to a widely used and accepted strategy in the clinical application of prognostic models, missing values were assumed to be normal. (87,88) Labile INR was defined as time within therapeutic range <60%. The therapeutic range was, according to clinical practice in Austria, between 2.0-3.0.

4.2 Statistical analysis

Data are presented as median and interquartile range for continuous data and absolute and relative frequency for categorical data, respectively.

Associations between increased HAS-BLED score (≥ 3) or VTE-BLEED score, respectively, and occurrence of major bleeding was evaluated using Fisher's exact test, due to the small number of events, and with minor bleeding using chi-square test. Odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated. SPSS 24 (IBM Corp., Armonk, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA) were used for data analysis; $P < 0.05$ was considered as significant. Numbers of major bleedings per 100 person years were calculated. Corresponding 95% CIs were calculated according to Ulm (1990). (89)

5 Results

One hundred-nineteen patients were screened for participation. Of these, seven were excluded as screening failure since their anticoagulant therapy was not for the indication of VTE, 1 patient died due to cancer before the first follow-up visit was performed. Characteristics of the remaining 111 patients included in the study are listed in Table 3. (85)

Table 3: Patient characteristics.

Characteristics*	N=111
Age, median	57.2 (17.6 – 87.1)
≥65years	42 (37%)
Female sex	58 (51%)
Body mass index, median	28.6 (18.0 – 43.0)
Arterial hypertension	48 (43%)
Abnormal renal function	18 (16%)
Abnormal liver function	0 (0%)
Stroke (history of)	3 (3%)
Prior bleeding	8 (7%)
Labile INR (52 patients on VKA)	11 (21%)
Co-medication (platelet inhibitors, non-steroidal anti-inflammatory drugs, immunosuppression)	18 (16%)
Alcohol or drug abuse [†]	2 (2%)
Malignancy	12 (11%)
Anemia	20 (18%)
Thrombocytopenia	4 (4%)
Heart failure	6 (5%)
HAS-BLED score at baseline visit <3 points	88 (79%)
≥3 points	23 (21%)

Reproduced from Rief P. et al. Calculation of HAS-BLED Score is useful for early identification of VTE patients at high risk for major bleeding events – A prospective outpatients cohort study. (85) With permission of “Seminars in Thrombosis and Hemostasis”. Abbreviations: INR, international normalized ratio; VKA, vitamin K antagonists. *Results are provided as n (%) or median (±interquartile range)

[†]Data of 1 patient was missing

Median duration of follow-up was 11.5 months. Of the patients included, 52 patients were treated with VKA, 20 with LMWH and 39 patients with NOAC. The high proportion of VKA treated patients included in the study is due to the start date of October 2014, when NOACs were rarely used for VTE therapy. Of VKA recipients, 21% had a labile INR during our follow-up period. (85)

Twenty-three patients (21%) were identified as high-risk of major bleeds by a HAS-BLED score of 3 points or higher. Four patients (4%; 4.2/100 person years, 95% CI 1.1-10.8) developed a major bleeding event. One out of 88 patients with a HAS-BLED score <3 had major bleeding compared to three out of 23 patients with HAS-BLED score ≥ 3 . Patients with HAS-BLED score ≥ 3 had an increased risk for major bleeding (OR 13.0; 95% CI: 0.9 - 692, $p = 0.028$) and a similar risk for minor bleeding (OR 2.2; 95% CI: 0.8 - 5.8, $p = 0.09$) compared to patients with a HAS-BLED score <3. (85)

Of the 4 observed major bleedings, 2 were gynecological, 1 was intracerebral and 1 was urologic; each bleeding event was spontaneous. Of these, 2 patients developed the major bleeding event while on anticoagulation with LMWH, 1 with VKA therapy (INR 3.2 at time of bleeding) and 1 on rivaroxaban. (85)

None of the major bleedings happened in the very early and acute setting of VTE treatment but during stable anticoagulant treatment. The patient on VKA treatment developed the major bleeding after 68 months of stable anticoagulation. The reason for long-term anticoagulation in this patient was multiple recurrent VTE events. Interestingly, this patient had the longest duration of anticoagulation before the bleeding event and a rather low HAS-BLED score of 2 points. The 2 major bleeds in patients on LMWH treatment occurred after 39 and 19 months, respectively. In the patient with rivaroxaban treatment the bleed occurred after 5 months. In none of those 4 patients was the bleeding fatal. Of the 55 minor bleedings, 13 were spontaneous skin hematomas, 15 recurrent spontaneous nose bleeding, 12 recurrent gum bleeds, 4 gastrointestinal (3 hemorrhoid bleedings, 1 minor bleeding from a gastric polyp) and 11 patients had combined minor bleedings (e.g. nose and gum bleeding etc.). Out of the 55 patients with minor bleedings, 15 had a HAS-BLED score ≥ 3 . (85)

In comparison, the VTE-BLEED score identified 37 patients (33%) as high risk (>2 points), of these 3 patients developed a major bleeding and 18 patients a minor bleeding event (Table 4).

Table 4: HAS-BLED and VTE-BLEED score.

	Total number of patients	Patients identified as high-risk	Major bleedings	Minor bleedings	OR for major bleeding in high-risk group	OR for minor bleeding in high-risk group
HAS-BLED score	111	23	3/23	15/23	OR 13.0; 95% CI: 0,9 - 692, p = .028	OR 2.2; 95% CI: 0.8 - 5.8, p = .09
VTE-BLEED score		37	3/37	18/37	OR 6.4; 95% CI: 0.5 - 342; p = .107	OR 0.9; 95% CI: 0.4 - 2.0; p = .89

Reproduced from Rief P. et al. Calculation of HAS-BLED Score is useful for early identification of VTE patients at high risk for major bleeding events – A prospective outpatients cohort study. (85) With permission of “Seminars in Thrombosis and Hemostasis”.

6 Discussion

In our study, we evaluated whether the HAS-BLED score could be incorporated as a tool for physicians guiding long-term anticoagulant therapy in patients with VTE and therefore find the optimal treatment regimen and duration of therapy. Our observational trial shows that in clinical practice, in a cohort of patients with long-term anticoagulation treated with a broad range of anticoagulants, a HAS-BLED score ≥ 3 indicated a significantly increased risk of major bleeding. Compared with a recently published VTE-BLEED score, both scores identify the same 3 out of 4 patients with major bleedings (true positive). A total of 18 false positive (no bleeding event) were identical for both algorithms. The HAS-BLED score had 3 further patients without major bleedings diagnosed with an increased risk (false positive) and the VTE-BLEED score 17 further patients. Overall, the number of false positive was lower in the HAS-BLED compared to the VTE-BLEED score, and the number of true positive was the same in our investigated cohort.

Major bleeding is the most important complication of anticoagulant therapy, occurring at a rate of 2.7 per 100 patient-years in VKA patients with the highest risk within the first week of treatment. (90-92) To assess the risk of bleeding complications during anticoagulant therapy in VTE patients, various different prediction models have been published, but their predictive value was reported to be rather poor, with C-statistics between 0.27 and 0.65. (43,64,73-75,77,78,93)

In summary 8 prediction models for bleeding complications in VTE patients can be found in the literature so far.

One is the computerized registry of patients with venous thromboembolism (RIETE). This is a large ongoing international registry of consecutive VTE patients. Ruiz-Gimenez et al. (73) so far enrolled 19,274 patients starting in 2008. The authors so far made an analysis of the incidence of major bleeding within three months of anticoagulation therapy. After that a bleeding risk prediction score on the basis of collected variables was published, the so called RIETE score. Univariate analysis showed 11 variables that were associated with an increased risk for major bleeding events. Afterwards the multivariate analysis confirmed 6 variables that were independently associated with an increased risk for major bleeding events: recent major bleeding, creatinine levels $>1.2\text{mg/dl}$, anemia, cancer, clinically overt

PE, age >75 years. The authors assigned 2 points for recent bleeding, 1.5 points for creatinine levels >1.2 mg/dl, 1.5 points for anemia and 1 point each for cancer, clinically overt PE and age > 75 years. The incidence of major bleeding was 0.3% in patients with 0 points, 2.6% in patients with 1-4 points and 7.3% in patients with >4 points. With that a bleeding risk index classification was done in 'low risk' (0 points), 'intermediate risk' (1-4 points) and 'high risk' (>4 points). In summary the authors published a risk score based on variables presented at clinical admission to identify VTE patients at low, mild or high risk for major bleeding events within the first three month of anticoagulant treatment. (73)

Another score published in this field is the Kuijer score. Kuijer et al. (74) constructed a bleeding risk score in 1999 based on variables and their odds ratios found in the literature. The resulting score was: $[1.6 \times \text{age}] + [1.3 \times \text{sex}] + [2.2 \times \text{malignancy}]$. 1 point was assigned each for age > 60 years, female sex and present malignancy. The evaluation of the scoring model was done in a patient test cohort first. Afterwards it was validated in a group of 780 patients. A subdivision in low-, moderate- and high-risk category was defined as follows: high risk (score >3 points), intermediate risk (1 to 3 points) and low risk (with a score of 0 points). The incidence of all bleeding complications in the first 3 months of anticoagulation was 17% together with 7% major bleedings. In patients assigned high risk bleeding rates were about 6 to 7 times higher than the rates observed in patients identified as low risk. (74)

Beyth et al. (75) developed the Outpatient bleeding risk index (OBRI) already in 1998. In this score one point was assigned for each of the following variables: Age 65 years or older, history of gastrointestinal tract bleeding, history of stroke, one or more comorbid conditions (myocardial infarction, anemia, renal impairment, and diabetes). Low risk was defined as a score of 0 risk points, moderate risk if the score was 1 or 2 points and high risk if the score was 3 or more. Years later the score was prospectively evaluated by Wells et al. (68). In this publication the authors observed 222 patients for a mean follow up time of 18.5 months and could demonstrate that the scoring model was able to discriminate between low- and moderate-risk groups for bleeding events. The rate of major bleeding was 4.3% in the moderate-risk group and 0% in the low-risk group. Only 2 patients of the 222 followed up were at high risk with only a minor hemorrhage in 1 of the 2 patients, so no rate of major bleeding in the high-risk group could be defined.

A very important recently published bleeding score is the VTE-BLEED score. Klok et al. (76) performed a post hoc analysis over 2553 VTE patients enrolled in the RE-COVER and RE-COVER II studies. These 2 studies compared dabigatran versus VKA for VTE treatment. They developed a model for prediction of major bleeding after day 30 of anticoagulation, so called “stable anticoagulation” in VTE patients. VTE-BLEED includes 6 independent variables: Active cancer (2 points); anemia (1.5 points); history of bleeding (1.5 points); >60 years age (1.5 points); renal dysfunction (1.5 points); uncontrolled arterial hypertension (1 point). With that, differentiation in 2 groups was done: A low risk group (0 – 1.5 points) with a bleeding incidence of 2.8% and an elevated risk group (> 2 points) with a bleeding incidence of 12.6%. The calculated odds ratio indicated a 5 times higher risk of bleeding for patients in the elevated-risk group. The c-statistic was 0.75 in dabigatran users and 0.59 in warfarin patients. (76)

The most recent ACCP-Guidelines (43), published in 2016 defined the following variables as risk factors for bleeding complications: Age > 65 years, age > 75 years, previous bleeding, cancer, metastatic cancer, renal failure, liver failure, thrombocytopenia, previous stroke, diabetes, anemia, antiplatelet therapy, poor anticoagulant control, comorbidity and reduced functional capacity, recent surgery, frequent falls and alcohol / NSAIDs abuse. A categorization scheme in low-risk (0 risk factors), moderate-risk (1 risk factor) and high risk (>1 risk factors) was estimated. The following table 5 shows the estimated absolute risk of major bleeding: (43)

Table 5: Estimated risk of major bleeding by Kearon Score / ACCP scheme

Categorization of Risk of Bleeding	Low Risk	Moderate Risk	High Risk
Anticoagulation 0-3 month			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6	3.2	12.8
Anticoagulation after first 3 month			
Baseline risk (%/year)	0.3	0.6	>2.5

Increased risk (%/year)	0.5	1.0	>4.0
Total risk (%/year)	0.8	1.6	>6.0

Reproduced from Kearon C. et al. (43) with permission of Elsevier.

The ACCP guidelines outline that the bleeding risk should be evaluated the first time after 3 months of anticoagulant treatment. Summarizing there is a strong need to identify patients with a high risk of major bleeding. Bleeding risk scores as a tool to help physicians guide their recommendation concerning anticoagulant treatment in VTE patients are of high importance. Once a high risk is recognized bleeding preventive strategies (e.g. in case of VKA treatment more frequent INR monitoring, exact control of hypertension or rapid laboratory controls of blood cell count and renal function) can be initiated by the treating physicians.

However, so far the scoring model suggested in these guidelines was not evaluated prospectively. (85)

The EINSTEIN trial evaluated rivaroxaban for treatment of acute VTE. Using data on >8000 patients enrolled in this trial, the EINSTEIN model (77) was derived. The reported c-statistic of the prediction model for major bleeding during the first 6 months was 0.68. Significant variables in this model were: older age, low hemoglobin level, active cancer, Black race and antiplatelet or non-steroidal anti-inflammatory drug therapy. (77) The Hokusai-VTE trial (78) enrolled 4118 VTE patients and compared edoxaban with warfarin. The Hokusai score was derived using data from these patients. Five variables were related with enhanced risk for major bleeding: female sex, concomitant antiplatelet therapy, hemoglobin <10 g/dL, history of hypertension, systolic blood pressure >160 mmHg. A c-statistic of 0.74 during the first 3 months of and 0.65 beyond 3 months of anticoagulation was reported. (78)

The HAS-BLED score was validated in multiple studies on a large number of atrial fibrillation patients and is recommended to be used in these patients. (72,82,83) The HAS-BLED risk score was established in 2010 by analyzing the data from the Euro Heart Survey from 3.978 participants. (72) It is a score based on eight parameters. HAS-BLED stands for: Hypertension / Abnormal renal and liver function / Stroke / Bleeding / Labile INR's / Elderly / Drugs or Alcohol. Therefore a score between 0 and 9 points is possible. (Table 6)

Table 6: HAS-BLED Score items (72)

HAS-BLED Score items	Points
Hypertension (systolic blood pressure >160 mmHg)	1
Abnormal liver function (history of cirrhosis, or bilirubin >2x the upper limit of normal in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase levels >3x the upper limit of normal)	1
Abnormal renal function (dialysis, serum creatinine values >200 µmol/L)	1
Stroke (history of)	1
Bleeding history or predisposition	1
Labile INR (time within therapeutic range <60%)	1
Age (≥65 years)	1
Drugs (use of platelet inhibitors or non-steroidal anti-inflammatory drugs)	1
Alcohol abuse	1

Abbreviations: INR, international normalized ratio. Reproduced from Pisters R. et al. (72) with permission of Elsevier.

Initially the score was developed to assess the 1-year risk for major bleeding complications in patients with atrial fibrillation and has been recommended within the European Society of Cardiology and Canadian guidelines. Lip et al. (94) validated the HAS-BLED score in 2011. In this publication a total of 7329 patients with atrial fibrillation and anticoagulant therapy were included. The HAS-BLED

score offered a better performance in predicting bleeding risk over previously published risk assessment schemes and was simpler to apply.

So far, 4 studies previously evaluated the HAS-BLED score in VTE patients for its predictive value concerning bleeding events. Two studies analyzed patients with VKA use for various indications (atrial fibrillation and VTE as well) and stated a C-statistic of 0.56 and 0.68 for the HAS-BLED Score. (93,95) Poli et al. (65) found a low C-statistic of 0.55 in patients aged over 80 years with VKA use.

Similar to this study, Kooiman et al. (66) recently showed that a HAS-BLED score of ≥ 3 is a strong predictor of major bleedings during VKA treatment for acute VTE in the first 6 months, despite a low sensitivity of 54.6%. They recommended that patients should be regarded as high risk by a cut-off of ≥ 3 points, leading to lower specificity (87.3%) on one hand, whilst avoiding missing a not negligible proportion of major bleeding events on the other. (85)

During recent years, 4 NOAC agents were established in the treatment of VTE patients. Due to their optimized bleeding profile and significant reduction in intracranial bleeding complications, these agents were approved by regulatory agencies and are nowadays treatment of choice in VTE patients. We therefore decided in the planning of our study to include patients treated with a wide range of anticoagulants to evaluate the performance of the HAS-BLED score in an entire clinical practice cohort. The incidences we found, together with findings from previous studies, support the predictive value of the HAS-BLED score in VTE patients. A score of 3 points or higher statistically significantly indicated a high risk for major bleeding events during a follow-up period of one year. (85)

The findings of our study support so far available data on the application of the HAS-BLED score in the clinical care of VTE patients. The HAS-BLED score may help physicians in their everyday practice making decisions on prolonged anticoagulant therapy and could improve the identification of high-risk patients concerning bleeding complications. Recommendations of recent published guidelines favor NOACs over VKA, especially due to a reduction of major bleeding complications. The recently published Einstein Choice study showed that patients on long-term anticoagulant treatment with rivaroxaban might benefit from a reduction of the dosage of rivaroxaban from 20 mg to 10 mg. (96) Similar findings

were already observed years ago in the Amplify Extension trial, in which a dose of 2.5 mg apixaban twice daily was similarly effective in preventing recurrence of VTE compared to a dosage of apixaban 5 mg BID, with significant decreased bleeds. (97) Particularly VTE patients with anticoagulation beyond 6 month of treatment and a HAS-BLED score of ≥ 3 , a change of anticoagulant treatment to a NOAC at a reduced dose as outlined above might be useful to prevent major bleeding complications. (85)

7 Conclusion

This study demonstrates that calculation of the HAS-BLED score in long-term anticoagulated patients after VTE may be a suitable tool to identify patients at high risk for major bleeding events. Since the HAS-BLED score was only examined for patients on VKA treatment so far, our observational trial was the first that evaluated the performance of the HAS-BLED score on VTE patients with long-term anticoagulation treated with a broad range of anticoagulants including NOACs. As recently published guidelines favor the use of NOAC over VKA in VTE treatment our results have a high practical impact.

We think that a dose reduction of anticoagulant agent (NOAC) should be considered in VTE patients on long-term anticoagulation and a HAS-BLED score ≥ 3 . This should be done together with clinical visits on a six-month basis as performed in this study. (85)

8 Limitations

Several limitations of the study should be mentioned: First, the number of patients included with ongoing anticoagulation is low and therefore the confidence intervals of our data are wide and cross the line of unity. Furthermore, the HAS-BLED score did not predict minor bleeds, which would have been expected as biologically plausible if the score predicts major bleeding. Therefore, studies in much larger

cohorts should be performed. Second, our study contains patients with different periods of preexisting duration of anticoagulant therapy. This may have contributed to a very low number of major bleeding events during the follow-up period, although the rate is similar to the rates reported in the literature previously. (81,86,90)

9 Future perspectives

Within the framework of the present study further parameters were collected, which were not yet evaluated when drafting this thesis.

Especially the collected laboratory parameters (e.g. cytochrome (CYP) 2C9 and 4F2, platelet count, hemoglobin level, serum creatinine etc.) might be of interest and could improve the performance of the HAS-BLED score by adding these parameters.

Furthermore, we still conduct follow-up visits on the patients enrolled in the study every six months. We therefore will be able to determine if the HAS-BLED score is helpful in predicting bleeding complications beyond 360 days of anticoagulant therapy.

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11 Appendix

Published Manuscript

Seminars in Thrombosis and Hemostasis

Rief P, Raggam RB, Hafner F, Avian A, Hackl G, Cvirn G, Brodmann M, Gary T.

Calculation of HAS-BLED Score is useful for early identification of VTE patients at high risk for major bleeding events – A prospective outpatients cohort study.

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