VENOUS AND ARTERIAL THROMBOTIC COMPLICATIONS

Solutions in clinical practice

Sake Johannes van der Wall

Venous and arterial thrombotic complications - solutions in clinical practice

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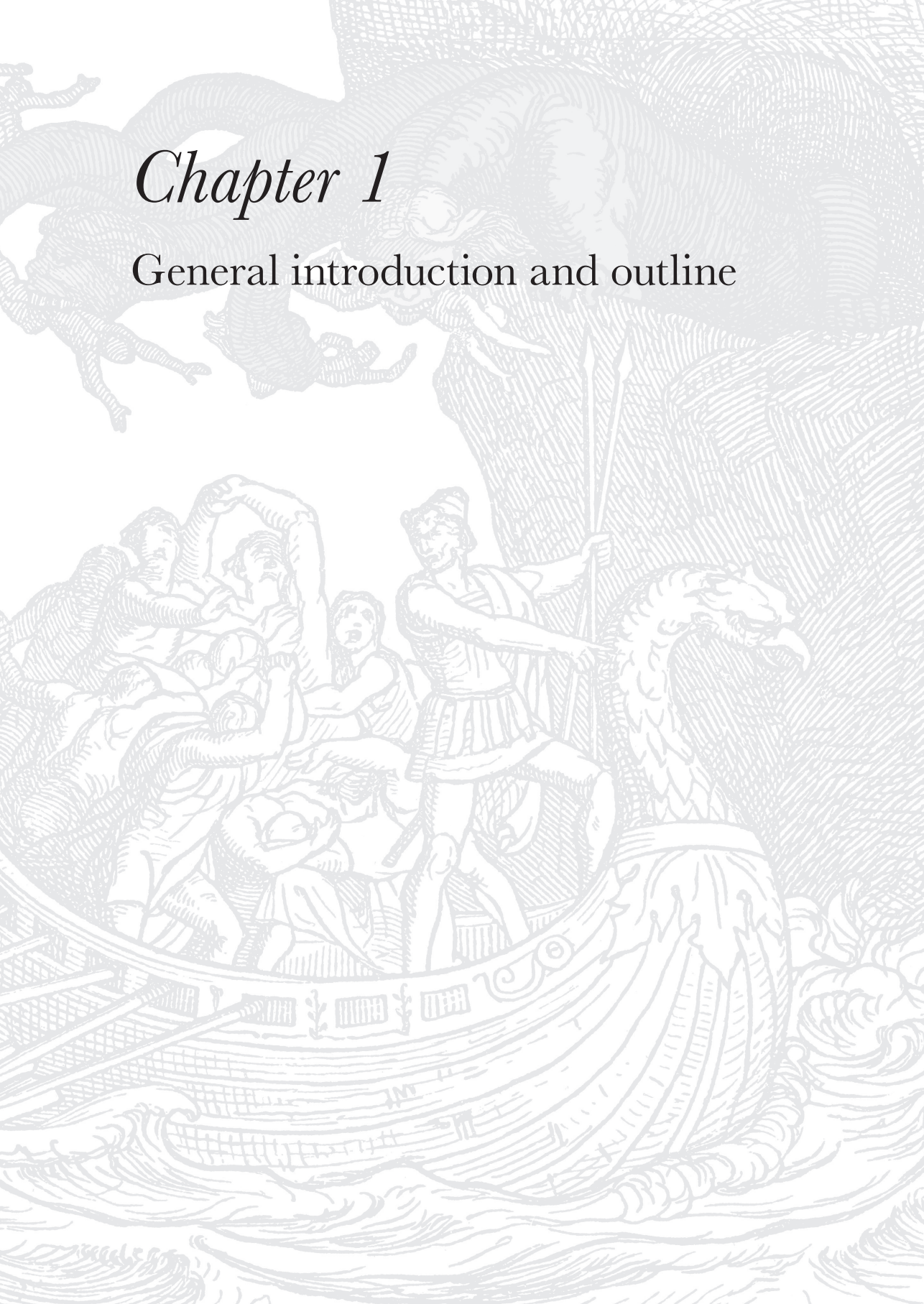

Chapter 1

General introduction and outline

Thrombosis is the formation of a blood clot that obstructs the blood flow through the circulatory system. Thrombosis can occur in veins and arteries. In the 19th century, Rudolf Virchow described the three factors necessary for the formation of thrombosis: blood stasis, changes in the vessel wall and hypercoagulability (1). While Virchow was referring to venous thrombosis, the same processes have been observed in arterial thrombosis. Both diseases have long been considered as separate entities, partly due to differences in mechanistic pathways as well as their distinct clinical presentation. Venous thrombosis occurs under low shear flow conditions due to alteration of blood stasis and composition, and is fibrin-rich due to the large amount of red blood cells (**Figure 1**) (2). Unlike venous thrombosis, arterial thrombosis occurs under high shear flow due to formation of platelet-rich thrombi around ruptured atherosclerotic plaques and damaged vascular endothelium. Venous thrombosis might lead to venous thromboembolism (VTE), while arterial thrombosis causes myocardial infarction and ischemic stroke. Traditional risk factors of venous thrombosis (e.g. surgery, immobilization and cancer) also differ from those that are associated with arterial thrombosis (e.g. smoking, obesity and diabetes). The separate nature of venous and arterial thrombosis has, however, been challenged by numerous reports, suggesting a closer link between both diseases (3-5).

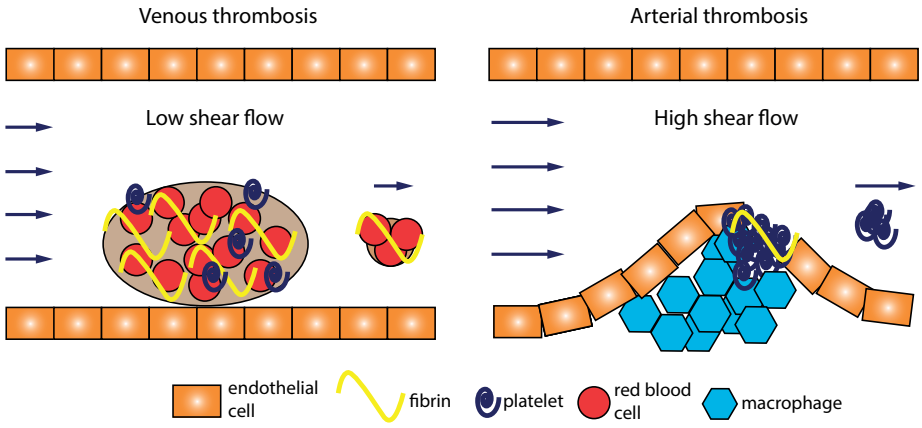

Figure 1. Pathophysiological differences between arterial and venous thrombosis. Figure adapted from Koupenova *et al.* (2017) (2)

The perceived difference between venous and arterial thrombosis is also reflected in the antithrombotic management. Oral anticoagulation is considered first-line treatment in fibrin-rich venous thrombi, whereas antiplatelet therapy is regularly recommended in platelet-rich arterial thrombi. Importantly, the use of antithrombotic drugs is associated with an increased risk of bleeding that potentially results in high risk of morbidity and mortality. Therefore, when deciding on antithrombotic treatment, the risk of thrombosis

should be equally weighed against the risk of bleeding. The appropriate antithrombotic treatment remains challenging and still has many grey areas. Importantly, both diseases are currently the leading causes of death in the Western parts of the world (6).

The first part of this thesis discusses VTE. For the individual patient, the risk of fatal recurrent VTE versus that of fatal bleeding is of particular relevance when deciding on the duration of therapeutic management. In **chapter 2**, the mortality risk of recurrent VTE is demonstrated after anticoagulation cessation in patients with initially unprovoked VTE. So far, these exact numbers were unknown for patients with unprovoked VTE, even though this knowledge is especially valuable for this specific patient category because of the recommendation for indefinite treatment duration, while patients with provoked VTE are generally treated for a short period of time (7, 8). Furthermore, VTE is frequent complication of cancer and cancer treatment (9). International guidelines currently recommend low-molecular-weight heparin (LMWH) therapy as first-line treatment because of a lower recurrence risk compared to the traditional therapy with vitamin K antagonists (VKA) (10). However, these daily subcutaneous LMWH injections may be burdensome owing to local pain or bruising, allergic reactions, or heparin-induced thrombocytopenia. In **chapter 3**, we prospectively assessed the discontinuation rate of these daily injections. The aim of **chapter 4** was to compare the discontinuation rate between two commonly used LMWH compounds – enoxaparin and nadroparin – in the same patient cohort as chapter 3.

The topic of the second part comprises prevention of arterial thrombosis after heart valve surgery. In patients undergoing bioprosthetic aortic heart valve implantation or mitral valve repair, patients are at risk of thromboembolism (11, 12). The optimal antithrombotic therapy after both procedures is still a matter of controversy. In **chapter 5** and **chapter 6** the rates of thromboembolic and bleeding complications are evaluated of two antithrombotic prevention strategies - VKA and aspirin - after bioprosthetic aortic valve implantation and mitral valve repair respectively.

The last part of the thesis focuses on idarucizumab for urgent dabigatran reversal. Dabigatran is a direct thrombin inhibitor that has a favorable risk-benefit profile compared to VKA for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation and treatment of patients with venous thromboembolism (13, 14). However, the lack of a reversal agent often has been considered as a hurdle for prescribing dabigatran. This has prompted the recent development of specific reversal agent idarucizumab for urgent dabigatran reversal in patients with uncontrolled or life-threatening bleeding or undergoing an emergency procedure (7). Because data on idarucizumab are scarce, **chapter 7** was aimed to determine the appropriateness of its usage as well as the hemostatic effectiveness and clinical outcome in daily practice. In **chapter 8,** dabigatran reversal by idarucizumab is discussed in patients presenting with major gastrointestinal (GI) bleeding, as evaluated in the RE-VERSE AD study (15).

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Part 1

Venous thromboembolism

Chapter 2

Fatal recurrent VTE after anticoagulant treatment for initial unprovoked VTE – a systematic review

S.J. van der Wall, L.M. van der Pol, Y.M. Ende-Verhaar, S.C. Cannegieter, S. Schulman, P. Prandoni, M. Rodger, M.V. Huisman, F.A. Klok

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ABSTRACT

Current guidelines recommend long-term anticoagulant therapy in patients with unprovoked venous thromboembolism (VTE). The risk of fatal recurrent VTE after treatment discontinuation (versus that of fatal bleeding during anticoagulation) is of particular relevance in the decision to continue or stop anticoagulation after the first three months. Our primary aim was to provide a point-estimate of the yearly rate of fatal recurrent VTE and VTE case-fatality rate in patients with unprovoked VTE after anticoagulation cessation. Data were extracted from both randomized controlled trials and observational studies published before May 1st 2017. The pooled fatality rates were calculated using a random-effects model. Eighteen studies with low to moderate bias were included in the primary analysis, totaling 6758 patients with a median follow up duration of 2.2 years (range 1-5 years). After anticoagulation cessation, the weighted pooled rate of VTE recurrence was 6.3 (95% CI 5.4-7.3) and the weighted pooled rate of fatal recurrent VTE was 0.17 (95% CI 0.047-0.33) per 100 patient-years, for a case-fatality rate of 2.6% (95% CI 0.86-5.0). These numbers are a solid benchmark for comparison to the risks associated with long-term anticoagulation treatment for the decision on the optimal duration of treatment of patients with unprovoked VTE.

INTRODUCTION

The risk of recurrent venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), persists after cessation of anticoagulant treatment and is particularly high among patients with unprovoked VTE (1-3). Consequently, recent treatment guidelines recommend continuation of anticoagulant therapy beyond the first three months in patients with unprovoked VTE without high risk for major bleeding (4-6). This recommendation is based on weighing the risk of recurrent VTE after anticoagulant treatment cessation against the risk of major bleeding during ongoing treatment. For the individual patient, the risk of fatal recurrent VTE versus that of fatal bleeding is of particular relevance when making the decision to prolong treatment or not.

The case-fatality rate of major bleeding events during long-term vitamin K antagonist (VKA) treatment has been estimated to be as high as 9%-13%, with a yearly rate of fatal bleeding varying between 0.2% and 1.5% (7, 8). Importantly, this bleeding risk was found to decrease considerably with the introduction of direct oral anticoagulants (DOACs) that are associated with lower rates of intracranial and fatal bleeding than VKA, while non-inferiority was shown with regard to risk of recurrent VTE (9).

The case-fatality rate of recurrent VTE after cessation of anticoagulant therapy has previously been shown to vary between 3.6% and 5.1% in a mixed cohort of patients with both provoked and unprovoked VTE, with a yearly risk of fatal recurrence ranging between 0.4% and 0.5% (7, 10). To date, these exact numbers are unknown for patients with unprovoked VTE, although this is the patient category for which this knowledge is most relevant (4, 5). Therefore, we conducted a systematic review and meta-analysis of the literature to provide an accurate point-estimate of the case-fatality rate of recurrent VTE as well as a yearly rate of fatal recurrences after anticoagulation cessation in patients with a first unprovoked VTE.

METHODS

Data sources and literature search

A systematic literature search was conducted for all relevant publications in PubMed, Embase, Web of Science and Cochrane in May 2017. The Subject Headings and/or keywords of our search strategy comprised 'Venous Thromboembolism', 'Pulmonary Embolism', 'Deep Venous Thrombosis', 'Anticoagulation' and 'Recurrence' and were database-specifically translated *(Supplementary Appendix)*.

Study selection and data extraction

Initial results were screened for relevant titles and abstracts by two independent reviewers (S.J. and L.M.). This process was performed in duplicate and disagreements were independently resolved by consensus or by a third reviewer (F.A.). Studies were included if: i) consecutive patients with objectively confirmed symptomatic DVT or PE were prospectively enrolled (proximal DVT diagnosed in case of evidence of thrombosis in the popliteal or more proximal veins on compression ultrasonography or contrast venography and a diagnosis of PE based on at least one subsegmental filling defect on computed tomography pulmonary angiography (CTPA), high-probability ventilation perfusion lung scan (V/Q) or abnormal pulmonary angiography, (ii) patients were dedicatedly followed for symptomatic recurrent VTE and such events were objectively confirmed, (iii) the initial anticoagulation treatment (with VKA or DOAC) was continued for at least three months and the follow-up period extended for at least three months after the anticoagulation therapy was discontinued, (iv) fatal VTE events during follow-up after treatment cessation were reported (PE and/or DVT) and (v) at least 100 patients were included. Only full-text publications in the English language were reviewed for potential inclusion. There was no restriction on publication year.

After selection of all relevant articles, two reviewers (S.J. and L.M.) independently extracted data on first author's name, year of publication, design (prospective/retrospective), number of patients included, age, initial anticoagulation treatment, the total duration of follow up after cessation of treatment, proportion of unprovoked VTE at baseline (PE/DVT), case-fatality rate of recurrent VTE during follow-up after anticoagulant discontinuation (PE/DVT) and finally overall mortality during follow-up, as reported by the authors. The authors of publications with missing data were approached by email at least two times on two weeks apart. The PRISMA statement for reporting systematic reviews and meta-analysis was used for this study (12).

Study objectives

The primary objective was to determine the case-fatality rate of recurrent VTE after anticoagulation cessation following a first unprovoked VTE diagnosis, as well as the yearly rate of fatal VTE recurrences from selected studies with low to moderate bias. The secondary aims were to determine the overall rate of fatal VTE for all available studies, including those with a high risk of bias, and to differentiate between: i) enrolment periods, comparing studies that started enrolment before and after the 1st of January 2000 (if reported), ii) cohort studies and RCTs, iii) studies with a follow-up duration that was shorter versus longer than 2.5 years, iv) patients who initially presented with DVT versus unprovoked PE and v) different definitions of fatal VTE that were applied.

Study outcomes and definitions

Recurrent PE was predefined as a new intraluminal filling defect on pulmonary angiography or CTPA, a new high probability perfusion defect on V/Q scan or any new defects after earlier normalisation of the scan (11). Recurrent DVT was defined as new non-compressibility by ultrasonography of the common femoral and/or popliteal vein, non-compressibility of a previously normalised vein segment, or a pronounced increase in vein diameter (≥ 4 mm) of a previously non-compressible venous segment (11). Patients with both index DVT and PE were classified as patients with PE when fatal rates were reported separately for this subgroup. Fatal recurrent VTE was predefined as PE diagnosed by autopsy, high-probability V/Q scan, a new intraluminal filling defect detected on pulmonary angiography, computed tomography (CTPA) or venography prior to death, or a high clinical suspicion as judged by the investigators of the individual studies. For each study, the definition of unprovoked VTE was evaluated post-hoc and compared to criteria provided by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (13).

Risk of bias

Two authors (S.J. and L.M.) independently evaluated the risk of bias at a study level in accordance with the Cochrane Collaboration's tool for assessing risk of bias and the PRISMA statement (12, 14). We focused on the following criteria: 1) pre-specified protocol, 2) clear description of inclusion and exclusion criteria, 3) adequate anticoagulation treatment prior to cessation according to international standards, 4) clear description of follow-up after anticoagulation cessation, 5) clear definitions provided of unprovoked and fatal VTE, 6) loss to follow up, 7) adjudication of outcomes, and 8) assessment of primary endpoint in all patients. Disagreements were resolved through discussion with a third author (F.A.).

Statistical analyses

Case-fatality rates of each study were calculated by dividing the number of recurrent fatal VTEs by all recurrent VTEs. The case-fatality rates were pooled after Freeman-Tukey double arcsine transformation to stabilize variances, using a random effects model according to the method of DerSimonian and Laird (15, 16). Pooled case-fatality rates were reported with corresponding 95% confidence intervals (CIs). Subsequently, we estimated the rate of recurrent VTE and fatal recurrent VTE per 100 patient-years. We assessed statistic heterogeneity of exposure effects across the various cohort studies by calculating the I^2 statistic, which depicts the variance of results from study to study beyond (or rather than) chance. Heterogeneity was considered low when I^2 was <25%, intermediate when I^2 was 25–75% and high when I^2 was >75% (17). Heterogeneity was explored using meta-regression. We evaluated differences across subgroups under the

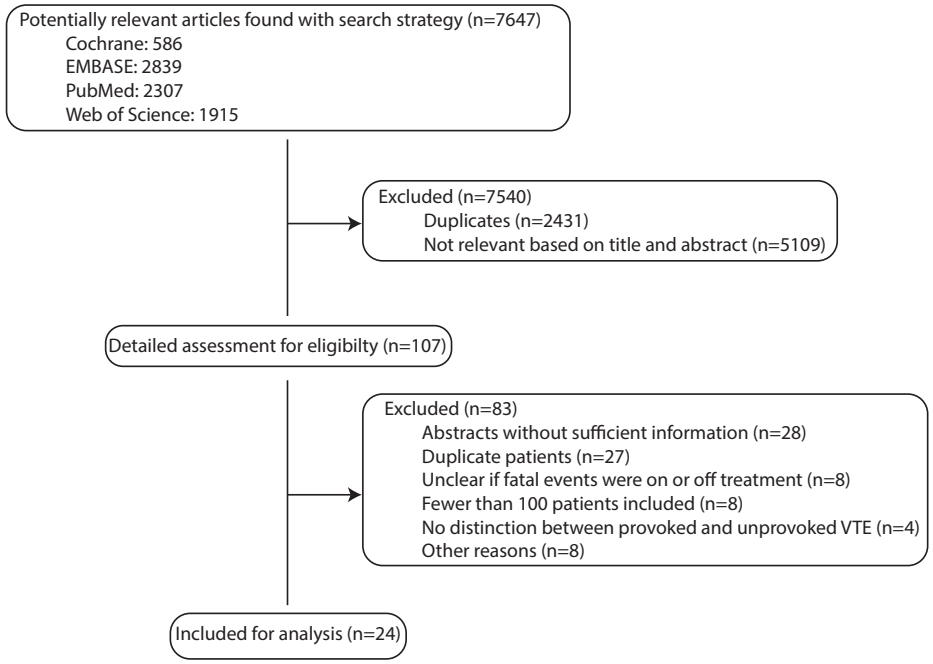
null hypothesis of no differences (χ^2 distribution with S (number of subgroups) minus 1 degree of freedom). All analyses were performed using Stata 14.0 (Stata Corp., College Station, TX, USA).

RESULTS

Literature search and study selection

The initial search yielded 7647 potentially relevant articles; 586 in Cochrane, 2839 in EMBASE, 2307 in PubMed and 1915 in Web of Science (**Figure 1**). After the first screening of title and abstract, 7540 records were excluded, leaving 107 unique articles for detailed assessment. An additional 83 articles were excluded after full review for the following reasons: 28 were abstracts only, with insufficient information, 27 comprised studies of duplicate patients with other reports, eight did not clarify if fatal events were on or off anticoagulation treatment, eight had fewer than 100 patients, four did not distinguish between provoked and unprovoked VTE and authors did not comply with our data request after at least two attempts, and eight were excluded for other reasons. The remaining 24 articles all satisfied our predetermined methodological criteria (18-41).

Figure 1. Flow-chart of the clinical search



Included studies

Table 1 shows the characteristics of the included studies. Fifteen were cohort studies (21, 23-26, 28, 29, 32, 33, 35, 37-41) and nine were RCTs (18-20, 22, 27, 30, 31, 34, 36). The 24 articles were published between 1995 and 2017 and included a total of 8914 patients with unprovoked VTE (range 117-914 patients per study). The median follow-up duration after treatment cessation was 2.5 years (range 1-7.7 years). The evaluation of the presence of bias is shown in **Table 2**. Of the 24 studies, 18 were considered to be at low or moderate risk of bias and were included in the primary analysis. Five studies did not involve an independent adjudication committee (24, 28, 32, 33, 40). Most studies did not meet the criteria of the ISTH definition of unprovoked VTE (20, 21, 24, 26, 28-30, 32, 34-39, 41). One study did not provide a definition of unprovoked VTE at all (22).

Primary outcome: rate of fatal recurrent VTE in studies with low or moderate risk of bias

The 18 studies with low or moderate risk of bias enrolled a total of 6758 patients with a median follow up of 2.2 years (range 133-914). **Table 3** shows the rates of recurrent VTE and fatal recurrent VTE per subgroup. The weighted pooled rate of recurrent VTE in studies with low or moderate risk of bias was 6.3 (95% CI 5.4-7.3; I^2=72.6%) per 100 patient-years and the rate of fatal recurrent VTE was 0.17 (95% CI 0.047-0.33; I^2=83.57%) per 100 patient-years, for a case-fatality rate of 2.6% (95% CI 0.86-5.0; I^2: 66.6%; **Figure 2**).

Secondary outcomes

The overall weighted pooled fatal rate of VTE recurrence among all 24 studies was 6.2 (95% CI 5.4-7.2; I^2=86.8%) per 100 patient-years and the rate of fatal recurrent VTE was 0.13 (95% CI 0.036-0.25; I^2=72.7%) per 100 patient-years, for a case-fatality rate of 2.0% (95% CI 0.69-3.8; I^2: 65.2%; **Supplementary Appendix, Figure S1**).

Studies that initiated enrolment before the year 2000 had a numerical higher but not significant different pooled rate of fatal VTE than studies that started inclusion within or after the year 2000 (0.27, 95%CI 0.038-0.59; I^2=83.1 vs. 0.039, 95%CI 0.0028-0.1 per 100 patient-years; I^2=0; P=0.70 for interaction), as well as case-fatality rate (3.7%, 95%CI 0.95-7.6; I^2=76.5 vs 0.71%, 95%CI 0.063-1.8; I^2=0; P=0.21 for interaction; **Supplementary Appendix, Figure S2**). Notably, the analysis of the more recent studies showed good homogeneity (both I^2=0) while the results of earlier studies were quite heterogeneous (I^2>75). The rate of fatal recurrent VTE was similar in cohort and RCT studies (0.11, 95% CI 0.009-0.29; I^2=79.5% vs. 0.14 95% CI 0.021-0.33; I^2=49.7% per 100 patient-years; P=0.96 for interaction) and studies with short and longer than 2.5 years follow up duration (0.11, 95% CI 0.018-0.27; I^2=52.4% vs. 0.13, 95% CI 0.076-0.35; I^2=81.7% per 100 patient-years; P=0.94 for interaction). Likewise, the case-fatality rates did not differ for cohort and RCT studies

Table 1. Characteristics and outcomes of the included studies.

Study, Year)	Study type	Enrolment period	VTE patients included	DVT patients included	PE patients included	Secondary VTE at baseline, no (%)	Initial treatment, minimum (months)	Follow up after cessation, years	Recurrent PE	Recurrent VTE, no. (DVT/PE at presentation)	Fatal VTE, no. (DVT/PE at presentation)
Schulman et al, 1995 [18]	RCT	1988-1991	289	249	40	0	VKA, 6	2	5	29 (24/5)	3 (2/1)
Agnelli et al., 2001 [19]	RCT	1995-1998	133	133	0	0	VKA, 3	3.1	3	21 (21/0)	0
Ridker et al., 2003 [20]	RCT	1998-2002	253	-	-	93 (37)	VKA, 3	2.1*	NA	37	2
Baglin et al.et al., 2003 [21]	Cohort	1997-2002	193	-	-	0	VKA, 3	2	NA	32	0
Schulman et al., 2003 [22]	RCT	1999-2000	611	389	221	98 (16)	VKA, 6	1.5	23	71	3
Cosmi et al., 2005 [23]	Cohort	1995-2004	400	400	0	0	VKA, 6	1.8[a]	15	75 (75/0)	5 (5/0)
Young et al., 2006 [24]	Cohort	1996-2002	103	103	0	Unclear	VKA, 3	2.9*	NA	26 (26/0)	1 (1/0)
Prandoni et al., 2007 [25]	Cohort	1991-2003	864	733	131	0	VKA, 6	4.2*[a]	NA	268 (240/28)	34 (30/4)
Baglin et al., 2008 [26]	Cohort	2001-2003	142	-	-	0	VKA, 6	3.2[a]	NA	28	0
Prandoni et al., 2009 [27]	RCT	1999-2006	151	151	0	0	VKA, 6	2.8	7	36 (36/0)	3 (3/0)
Poli et al., 2010 [28]	Cohort	Unclear	161	0	161	0	VKA, 6	3*[a]	11	20 (0/20)	0
Siragusa et al., 2011 [29]	Cohort	1999-2007	409	409	0	0	VKA, 3	1	NA	29 (29/0)	0
Becattini et al., 2012 [30]	RCT	2004-2010	197	130	67	0	VKA, 6	2[a]	14	43 (27/16)	1 (0/1)
Brighton et al., 2012 [31]	RCT	2003-2011	411	232	175	0	VKA, 3	3.1*[a]	NA	73 (40/33)	1 (0/1)
Olie et al., 2012 [32]	Cohort	2003-2009	583	175	421	0	VKA, 8 (mean)	2.2	NA	74 (21/53)	0
Ribeiro et al., 2013 [33]	Cohort	2000-2011	117	88	29	0	VKA, 6	3.6*	NA	22 (20/2)	0
Schulman et al., 2013 [34]	RCT	2006-2010	662	441	213	Unclear	DOAC or VKA, 6	1.5	13	35 (22/13)	0
Galanaud et al., 2014 [35]	Cohort	2004-2006	173	173	0	0	DOAC or VKA, 3	3	NA	18 (18/0)	2 (2/0)
Couturaud et al., 2015 [36]	RCT	2007-2012	187	0	187	0	VKA, 6	3.4[a]	31	39 (0/39)	0
Kearon et al., 2015 [37]	Cohort	2008-2012	319	141	178	16 (5)	VKA, 3	2.2*	17	42 (20/22)	1 (0/1)
Rodger et al., 2016 [38]	Cohort	2001-2006	450	221	229	0	DOAC or VKA, 5	5	NA	161 (105/56)	3 (3/0)
Kyrle et al., 2016 [39]	Cohort	1992-2008	839	503	336	0	VKA, 7 (mean)	7.7[a]	116	259 (151/108)	4 (3/1)
Moreno et al., 2016 [40]	Cohort	2004-2013	353	83	270	0	VKA, 3	1.8[a]	43	65	1
Rodger et al., 2017 [41]	Cohort	2008-2015	914	260	654	Unclear	DOAC or VKA, 5	1	NA	42 (10/32)	0

Note: DVT=Deep Vein Thrombosis, PE=Pulmonary Embolism, VTE=Venous Thromboembolism, RCT=Randomised Controlled Trial, VKA=Vitamin K Antagonist, DOAC=Direct Oral Anticoagulant, NA=Not Applicable. * Comprises follow up of patients with provoked VTE. [a] Median follow up duration

Table 2. Evaluation of presence of bias for all 24 identified relevant studies.

	Assessment of bias								
	Representative study population			Incomplete outcome data		Selective outcome reporting			Overall judgement
Article	Clear description in and exclusion criteria	Patient population	Adequate anticoagulation treatment prior to cessation	Clear follow up duration	Complete follow up >95%	Definition of unprovoked VTE	Definition of fatal VTE	Adjudication of outcomes	Bias in certain direction
Schulman et al., 1995 [18]	●	●	●	●	●	●	●	●	●
Agnelli et al., 2001 [19]	●	●	●	●	●	●	●	●	●
Ridker et al., 2003 [20]	●	●	●	●	●	●	●	●	●
Baglin et al., 2003 [21]	●	●	●	●	●	●	●	●	●
Schulman et al., 2003 [22]	●	●	●	●	●	●	●	●	●
Cosmi et al., 2005 [23]	●	●	●	●	●	●	●	●	●
Young et al., 2006 [24]	●	●	●	●	●	●	●	●	●
Prandoni et al., 2007 [25]	●	●	●	●	●	●	●	●	●
Baglin et al., 2008 [26]	●	●	●	●	●	●	●	●	●
Prandoni et al., 2009 [27]	●	●	●	●	●	●	●	●	●
Poli et al., 2010 [28]	●	●	●	●	●	●	●	●	●
Siragusa et al., 2011 [29]	●	●	●	●	●	●	●	●	●
Becattini et al., 2012 [30]	●	●	●	●	●	●	●	●	●
Brighton et al., 2012 [31]	●	●	●	●	●	●	●	●	●
Olie et al., 2012 [32]	●	●	●	●	●	●	●	●	●
Ribeiro et al., 2013 [33]	●	●	●	●	●	●	●	●	●
Schulman et al., 2013 [34]	●	●	●	●	●	●	●	●	●
Galanaud et al., 2014 [35]	●	●	●	●	●	●	●	●	●
Couturaud et al., 2015 [36]	●	●	●	●	●	●	●	●	●
Kearon et al., 2015 [37]	●	●	●	●	●	●	●	●	●
Rodger et al., 2016 [38]	●	●	●	●	●	●	●	●	●
Kyrle et al., 2016 [39]	●	●	●	●	●	●	●	●	●
Moreno et al., 2016 [40]	●	●	●	●	●	●	●	●	●
Rodger et al., 2017 [41]	●	●	●	●	●	●	●	●	●

Note: VTE=Venous Thromboembolism

Overall
- ● unknown or unclear
- ● no
- ● yes

Definition unprovoked/fatal VTE
- ● other than definitions in our study
- ● not present
- ● according to definitions in our study

Overall risk of bias
- ● high risk
- ● moderate risk
- ● low risk

Patient population: patient selection
- ● no distinction in follow up and baseline characteristics between provoked and unprovoked VTE
- ● no distinction in follow up or baseline characteristics between provoked and unprovoked VTE
- ● unprovoked VTE patients clearly identified

Table 3. Fatal VTE rates per subgroup.

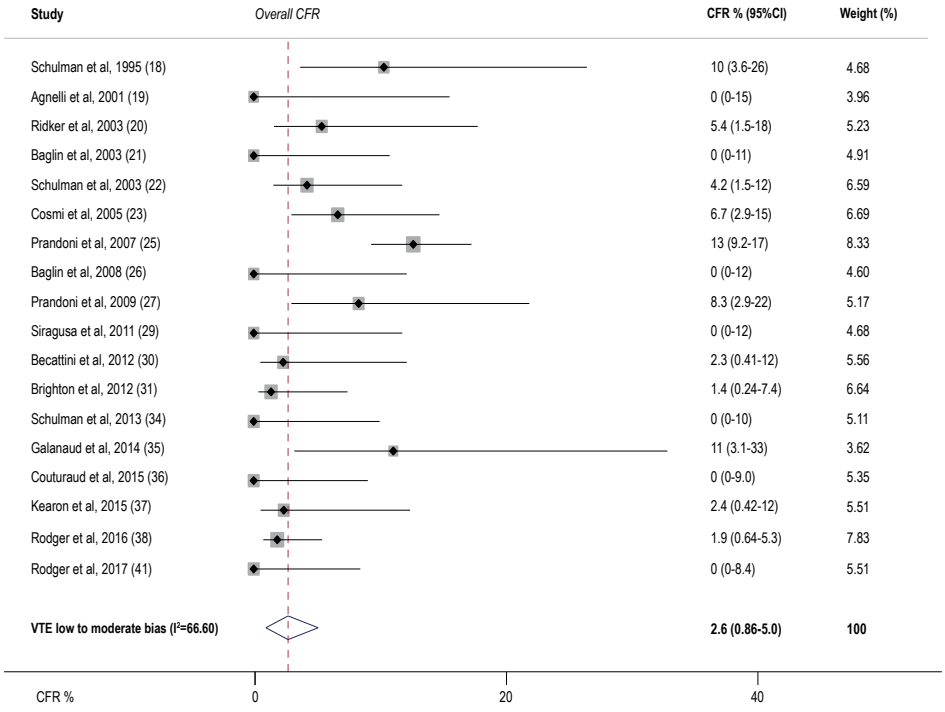
Subgroup	Studies included (n)	Patients (n)	Fatal recurrent VTE (n)	Recurrent VTE (n)	Pooled Case-fatality rate % (95%CI)	I^2 (%)	Pooled rate of recurrent fatal VTE (95%CI), events per 100 py	Pooled rate of recurrent VTE (95%CI), events per 100 py
VTE at baseline in studies with low or moderate risk of bias								
Unprovoked VTE	18	6758	58	1079	2.6 (0.86-5.0)	66.60	0.17 (0.047-0.33)	6.3 (5.42-7.3)
Unprovoked DVT	13	3675	45	669	2.7 (0.50-6.1)	63.52	0.18 (0.025-0.43)	6.2 (4.6-8.0)
Unprovoked PE	9	1783	8	243	1.6 (0-5.7)	48.43	0.060 (0-0.28)	5.6 (4.2-7.1)
Other subgroups								
Overall VTE	24	8914	64	1545	2.0 (0.69-3.8)	65.21	0.13 (0.036-0.25)	6.2 (5.4-7.2)
Overall DVT	17	4544	49	887	2.3 (0.52-4.8)	60.39	0.14 (0.022-0.33)	6.3 (5.0-7.6)
Overall PE	13	2730	9	426	0.12 (0-1.8)	34.90	0.011 (0-0.11)	4.9 (4.2-5.7)
Enrolment before 2000	11	4245	55	883	4.0 (1.3-7.8)	76.46	0.27 (0.038-0.59)	6.8 (5.4-8.4)
Enrolment after 1st of Jan 2000	12	4508	9	642	0.71 (0.063-1.8)	0	0.039 (0.0028-0.1)	5.9 (0.47-7.2)
Cohort	16	6020	51	1161	1.7 (0.19-4.2)	74.62	0.11 (0.009-0.29)	6.4 (5.3-7.6)
RCT	9	2894	13	384	2.5 (0.69-5.0)	26.83	0.14 (0.021-0.33)	6.0 (4.6-7.6)
FU ≤2.5 years	12	5183	16	574	1.8 (0.46-3.8)	34.85	0.11 (0.018-0.27)	6.7 (5.2-8.3)
FU >2.5 years	12	3731	48	971	2.2 (0.22-5.4)	76.57	0.13 (0.076-0.35)	5.8 (4.8-7.0)

Note: VTE=Venous Thromboembolism, DVT=Deep Vein Thrombosis, PE=Pulmonary Embolism, RCT=Randomised Controlled Trial, FU=Follow Up, CI=Confidence Interval, py=patient years.

(1.7%, 95% CI 0.19-4.2; I^2=74.6% vs. 2.5%, 95% CI 0.69-5.0; I^2=26.8%; P=0.87 for interaction) as well as for studies with shorter and longer than 2.5 years follow up duration (2.2%, 95% CI 0.22-5.4; I^2=76.6% vs. 1.8%, 95% CI 0.46-3.8; I^2=34.9%; P=0.69 for interaction).

In 19 studies, fatal recurrent VTE could be distinguished for patients initially presenting with DVT versus PE (13, 18, 19, 23-25, 27-39, 41). The case-fatality rates of patients initially presenting with DVT and PE were 2.3% (95% CI 0.52-4.8; I^2=60.39%) and 0.12% (95% CI 0-1.8; I^2=34.9%; P=0.57 for interaction; **Supplementary Appendix, Figure S3**). When focussing on studies with low or moderate risk of bias only, this numerically difference decreased considerably (2.7% (95% CI 0.50-6.1; I^2=63.52%) versus 1.6% (95% CI 0-5.7; I^2=48.43%); P=0.66 for interaction; **Supplementary Appendix, Figure S4**).

Figure 2. Meta-analysis of the case-fatality incidences after anticoagulant cessation in studies with low to moderate risk of bias.



Note: CFR=Case Fatality Rate, CI=Confidence Interval.

Fatal VTE definition

The definition of fatal VTE varied widely across studies (**Supplementary Appendix, Table S1**). Only twelve studies (54%) actually reported a definition of fatal VTE (18, 19, 22, 24, 25, 27, 30, 31, 34, 36-38), of which eleven (92%) included autopsy and/or clinical sus-

picion (18, 19, 22, 24, 25, 27, 30, 31, 36-38) and five (42%) involved 'sudden unexplained death' (25, 27, 34, 36, 37). Studies including 'sudden unexplained death' in their fatal VTE definition were found to have the highest case-fatality rates (3.6%, 95% CI 0.018-11; I^2= 81.15%), while studies without a clear definition of fatal recurrent VTE reported lowest rates (0.95%, 95% CI 0.067-2.5; I^2= 27.06%; P=0.29 for interaction) **Supplementary Appendix, Table S2**). This difference in case-fatality rates was observed in both index PE and index DVT patients.

DISCUSSION

In this systematic review and meta-analysis, we determined the risk of fatal recurrent VTE in patients with unprovoked VTE after cessation of anticoagulation treatment. We observed a pooled rate of fatal recurrent VTE of 0.17 per 100 patient-years with a case-fatality rate of 2.6% in studies with low to moderate risk of bias. Where most meta-analyses performed in our study showed relevant heterogeneity among the included studies, the secondary analysis focussing on more recent studies (patient enrolment after January 1st 2000, total of 4508 patients) showed good homogeneity. The numerically lower pooled rate of fatal recurrence (0.039 per 100 patient-years) and case-fatality rate (0.71%) found in this subanalysis may be explained by improved patient care over the years, earlier presentation at the hospital or detection of smaller and less dangerous PE blood clots by more advanced CTPA technology.

The present study revealed similar rates of fatal recurrent VTE in cohort studies compared to RCTs, thus supporting the external validity of our findings. The fatal rates of studies with longer and shorter follow-up durations did not differ as well, indicating that our main finding is valid for long-term follow-up (at least beyond the first two years after treatment continuation). Further, we use the finding of a lower rate of fatal recurrent VTE in more recent studies as an argument to hypothesize that the identified rates in our main analysis represent an overestimation of the 'true' risk rather than an underestimation. Therefore, our findings provide clinicians, guidelines committees, investigators and policymakers with a solid and valid benchmark of the mortality risk due to recurrent VTE after cessation of treatment to be compared with the risks associated with long-term anticoagulation treatment for patients with unprovoked VTE (4, 5). Importantly, since risk of VTE recurrence changes over time with the bulk of recurrences occurring in the first years, and the risk of bleeding remains more stable, the ultimate answer to the question of the most optimal duration of anticoagulation for unprovoked VTE is to be determined in future RCTs with long-term follow-up.

We found a non-significant higher risk of fatal recurrent VTE after an index DVT diagnosis than after an index PE diagnosis which was unexpected (7, 10). This difference is

mostly explained by biases of the data pooling due to major methodological differences between the included studies. Other explanations may be that PE is often over diagnosed due to adoption of more and more advanced CT technology (42). In addition, a selection of 'healthier' PE patients for whom anticoagulation discontinuation was deemed to be safe in observational studies could have contributed to the lower observed fatal rates of recurrent VTE. Lastly, many of the patients with DVT may actually have had PE as well, although this was not objectively confirmed and therefore nor reported in the original study publications.

Remarkably, the reported rate of fatal recurrent VTE was largely dependent on the definition adopted across the various studies. Overall, studies without a clear definition reported the lowest rates, whilst studies in which unexplained death was adjudicated as recurrent VTE showed the highest rates. Half of the included studies did not report a definition of fatal VTE, whereas the remaining studies used various definitions ranging from autopsy findings alone to 'sudden unexplained death'. With no widely accepted definition of 'fatal VTE', it is impossible to rank these different definitions, although it seems reasonable to assume that studies focussing on autopsy findings may provide underestimated rates of fatal recurrent VTE, while the opposite is true for studies adjudicating all unexplained death as being provoked by recurrent VTE. Moreover, the adjudication process itself might also be difficult and could possibly lead to different rates of PE-related deaths among studies. Our findings thus urgently call for an effort to standardize this definition for future studies in order to allow for valid inter-study comparisons (43).

Current guideline recommendations with regard to extended duration of treatment after unprovoked VTE will be confirmed beyond doubt if these studies show that long-term treatment with DOACs is, indeed, associated with a yearly rate of fatal bleeding lower than 0.047-0.33%. Until then, anticoagulation duration should be individualised based on a patient-specific balance between bleeding and recurrent thrombotic risk. Valid bleeding and thrombotic risk tools have been developed and -although not validated in RCTs- could be helpful to assess these risks and thereby identify patients who may benefit from short or long-term anticoagulation treatment (44-47).

Strong points of this analysis include the strict selection criteria applied and the large number of patients studied. Source data were only derived from high-quality studies. Moreover, we were able to compare fatal rates in four relevant subgroups. Our study has several limitations in addition to the issue of varying definitions of fatal recurrent VTE. In particular, we did not have the availability of patient-level data, which would have allowed us to evaluate the prognostic role of risk factors such as age and gender. Also, although we performed rigorous inclusion criteria and focused only on high-quality studies, the meta-analyses presented were subject to relevant heterogeneity caused by

several between-study differences, especially for those studies that enrolled patients before January 1st 2000.

Conclusions

This meta-analysis revealed a pooled rate of fatal recurrent VTE of 0.17 (95% CI 0.047-0.33) per 100 patient-years for patients with unprovoked VTE after discontinuation of anticoagulation therapy in studies with low to moderate risk of bias. This was consistent with a case-fatality rate of 2.6% (95% CI 0.86-5.0). Notably, we observed utilisation of varying fatal VTE definitions which was associated with moderate to high between-study heterogeneity, affecting the reported rates of fatal recurrent VTE. Current guideline recommendations on the duration of treatment of unprovoked VTE would be strengthened if future studies show that long-term anticoagulation treatment with DOACs is indeed associated with a rate of fatal bleeding lower than 0.33% per year, representing the upper limit of the 95% confidence interval the pooled incident rate of fatal recurrent VTE after anticoagulation discontinuation.

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Chapter 3

Continuation of LMWH treatment for cancer related venous thromboembolism – a prospective cohort study in daily clinical practice

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ABSTRACT

Background

Current guidelines recommend low-molecular-weight-heparins (LMWH) monotherapy for 3 to 6 months as first-line treatment for cancer-associated venous thromboembolism (VTE). However, although daily administration of LMWH injections over a course of several months may be burdensome, the number of patients who quit because of LMWH side effects is unknown.

Objectives

The aim of this study was to evaluate the continuation rate and complications of daily LMWH injections in cancer-associated VTE.

Methods

Consecutive patients with active cancer and objectively confirmed symptomatic proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE), treated at three Dutch hospitals and one Spanish hospital, were included to evaluate adherence to LMWH therapy during LMWH treatment. Patients were excluded when they received other anticoagulants, were lost to follow up or experienced a venous catheter-associated thrombosis.

Results

A total of 372 patients were analysed during LMWH treatment with a maximum of 180 days. The cumulative incidence of discontinuation was 21% (95% confidence interval (CI): 17-25) after a median period of 90 days (interquartile range 60-120 days). Only female sex was found to be significantly associated with premature LMWH discontinuation (OR 1.6; 95%CI 1.03-2.5). Thirty patients (8.1%) developed recurrent VTE, 30 patients (8.3%) suffered a major bleeding and 106 patients (28%) died.

Conclusion

Our study reveals that one out of five patients with cancer-associated VTE stopped LMWH injections because of side effects. This finding provides relevant background information to current clinical trials investigating the efficacy and safety of direct oral anticoagulants (DOACs) compared to LMWH.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent complication of cancer and cancer treatment (1). Moreover, the treatment of cancer-associated VTE is challenging because cancer patients display a substantially high risk of recurrent VTE as well as major bleeding complications (2, 3).

Low-molecular-weight heparins (LMWH) are recommended for at least three to six months as first-line treatment for cancer-associated VTE by most current international guidelines because of proven superior efficacy compared to conventional vitamin K antagonists (VKA), with comparable risk of major bleeding (4-6). Treatment with LMWH consists of daily subcutaneous self-injections, often in an ambulatory setting. Administration of LMWH therapy over a course of several months may be burdensome due to local pain or bruising linked to the subcutaneous injection allergic reactions, or less frequently heparin-induced thrombocytopenia. Pain and skin hematoma at the injection site are the most common adverse side effects in daily practice, occurring in up to 90% of subjects with self-administration (7). Studies investigating the efficacy of long-term LMWH use in cancer patients found discontinuation rates varying from 33% to 58% after three to six months, because of complications including recurrent VTE, bleeding or death (8-10). Further, in recent studies 11% to 20% of cancer patients switched from LMWH injections to oral anticoagulants within three to six months, possibly due to avoid discomfort of injections or due to a lack of communication among health professionals or a deliberate physician's decision (11-13). Thus, detailed information about the burden of daily subcutaneous injections is required.

More accurate knowledge of the tolerability of long term use of LMWH in cancer patients with VTE is very relevant when considering optimal management of this specific patient category, in particular with the advent of the direct oral anticoagulants (DOACs) that may offer a more attractive treatment option (14). We set out an observational study to evaluate the continuation rate and complications of daily LMWH injections in cancer patients with VTE in daily clinical practice.

METHODS

Patients

This was a prospective, multi-center, cohort follow-up study of consecutive patients with active cancer and objectively confirmed symptomatic proximal DVT and/or PE to evaluate adherence to LMWH therapy during LMWH treatment with a maximum of 180 days. Patients from three Dutch hospitals (Leiden University Medical Center, Alrijne

Hospital Leiden and Leiderdorp) and one Spanish Hospital (Ramon y Cajal Hospital, IRYCIS) diagnosed with cancer-associated VTE between 2004 and 2014 and treated with therapeutic doses of LMWH were eligible for inclusion. We defined active cancer in accordance with previous studies on this subject (4): a histologically confirmed solid tumor or hematological malignancy diagnosed or treated during the previous six months, recurrent or metastatic cancer, or cancer in palliative stages with the exception of basal cell or squamous-cell carcinoma of the skin.

Proximal DVT was diagnosed in case of evidence of thrombosis in the popliteal or more proximal veins on compression ultrasonography or contrast venography (15). A diagnosis of PE was based on at least one subsegmental filling defect on computed tomography pulmonary angiography (CTPA), high-probability ventilation perfusion lung scan or abnormal pulmonary angiography (15). In the LUMC and Alrijne Hospital patients were treated with weight-adjusted doses of subcutaneous nadroparin, either given once or twice daily - Fraxodi was given by 11,400 IU once daily (OD) for patients under 70 kg and 15,200 IU OD for patients above 70 kg; Fraxiparine was given 5700 IU twice daily (BID) for patients under 70 kg and 7600 IU BID for patients 70 kg or more. In Spain, patients received enoxaparin 1mg/kg BID in the first month followed by a dosage of 1,5mg/kg OD.

Patients with an upper extremity DVT associated with a central venous catheter (CVC) were ineligible because of the recommended limited anticoagulant treatment duration of four weeks after removal of the central venous catheter. The institutional review board of both the LUMC and the Ramon y Cajal Hospital IRYCIS approved the study and waived the need for informed consent due to the observational design.

Study endpoints and follow up procedures

The primary objective of this study was to establish the frequency of LMWH discontinuation because of LMWH side effects. Reason for discontinuations were noted and categorized as follows: local side effects defined as hematomas at injection side, site pain and exanthema, and heparin induced thrombocytopenia. Secondary objectives were (a) to identify risk factors for LMWH discontinuation, (b) to determine the incidence rates of recurrent VTE, major bleeding and mortality during the follow-up period and (c) to identify risk factors for mortality. Predefined candidate predictors for discontinuation and mortality were defined as age, sex, anemia (defined as hemoglobin level less than 7,5 mmol/L for women and less than 8,5 mmol/L for men), impaired kidney function (defined as a glomerular filtration rate below 60 mL/min/1.73m^2 estimated with the Modification of Diet in Renal Disease (MDRD) equation), thrombocytopenia (defined as a platelet count below 150x10^3/L), type of cancer (solid versus hematologic), metastatic disease, immobilization (for at least three consecutive days) four weeks before the VTE

event and previous use of anticoagulation therapy. These risk factors were assessed at baseline in all patients.

All patients were followed were followed during LMWH treatment with a maximum of 180 days, in which they visited the outpatient clinic on a regular basis for their oncological treatment. Our endpoints were assessed at all these scheduled visits as well as during intercurrent hospitalization by standardized assessment of LWMH compliance and signs and symptoms of recurrent thromboembolism and bleeding episodes.

Recurrent PE was defined as a new intraluminal filling defect on pulmonary angiography or CTPA, a new high probability perfusion defect on V/Q scan or any new defects after earlier normalization of the scan, or confirmation of a new PE at autopsy. V/Q-scans were evaluated according to the PIOPED criteria. Recurrent lower extremity DVT was defined as new non-compressibility by ultrasonography of the common femoral and/or popliteal vein for lower extremity DVT in the transverse plane or the vein diameter under maximum compression, as measured in the abnormal venous segment, showing enlargement of thrombus diameter (>4mm). Major bleed was defined in accordance with the International Society of Thrombosis and Haemostasis criteria (16). Cause of death was verified by reviewing the pathology report. If autopsy was not performed, the likely cause of death was verified with the treating physician by reviewing the medical records and death certificates.

Statistical analyses

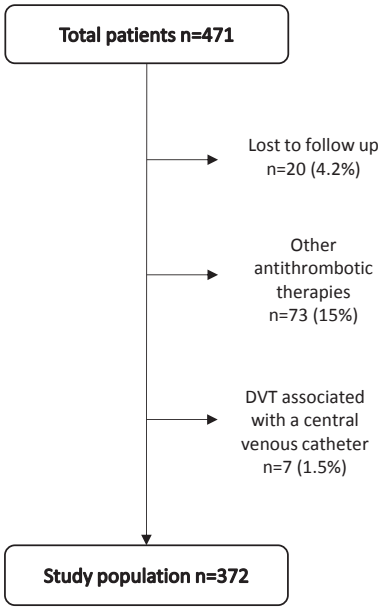
We used means (standard deviation (SD)) and medians (interquartile range (IQR)) to present baseline continuous baseline variables. For categorical variables, we used frequencies and percentages. For analysis of primary and secondary endpoints, follow-up started at the moment of first LMWH administration and ended at time of LMWH discontinuation, death or maximum follow-up period of 180 days. The cumulative incidences of LMWH discontinuation, recurrent VTE, major bleeding and death were estimated according to the Kaplan-Meier method applying a competing risk analysis, and presented with two-sided 95% confidence intervals (CI) (17). We performed a backward selection multivariate analysis using Cox regression methods to evaluate possible predictors for LMWH cessation and mortality. Data were analyzed using SPSS version 22 (SPSS inc., Chicago IL). A p-value <0.05 was considered significant.

RESULTS

Patients

During the study period, 466 patients were diagnosed with cancer-associated VTE, of whom 94 were excluded for the following reasons – other forms of anticoagulant therapy, lost to follow-up and catheter-related thrombosis, leaving 372 patients for the current analysis (**Figure 1**). **Table 1** shows an overview of baseline characteristics of the included patients. Their mean age was 67 years (SD 13); 204 (55%) were male; and half of patients had metastatic cancer. The majority of 339 (91%) patients had solid tumors, 19 (5.1%) patients had a hematologic malignancy and in 14 patients the type of cancer was unknown.

Figure 1. Flowchart of the study population.



Note: DVT=Deep Vein Thrombosis

Primary endpoint: LMWH discontinuation

A total of 194 (51%) patients discontinued LMWH treatment within six months; of whom 78 (21%) patients stopped because of LMWH side effects. Unacceptable pain at the injection site was the most common reason of discontinuation, occurring in 33 patients (8.9%); 27 patients (7.3%) had large local injection site hematomas; 15 patients (4%) were found to have allergic reactions (local irritation or generalized exanthema) and three patients (0.81%) developed heparin induced thrombocytopenia. The Kaplan Meier survival curve for discontinuation because of side effects per competing risk analysis is shown in **Figure 2**. LMWH treatment was stopped after a median duration of 90 days (interquartile range 60-120 days). The cumulative incidence (per competing risk analysis) of discontinuation during six months of LMWH treatment was 21% (95%CI 17-25).

Predictors for LMWH discontinuation

Female sex was found to be significantly associated with premature LMWH discontinuation because of side effects (odds ratio (OR) 1.6; 95%CI 1.03-2.5) while both disease stage as well as co-morbid conditions were not (**Table 2**). Multivariate analysis confirmed the association between female sex and LMWH discontinuation (adjusted OR 1.7; 95%CI 1.1-2.8), and did not identify additional independent predictors.

Recurrences, bleeding and mortality

Thirty patients were diagnosed with recurrent VTE during LMWH treatment, for an 8.1% (95%CI 5.4-11) cumulative incidence (per competing risk analysis); of these patients 14 suffered a fatal VTE (47%). Major bleeding occurred in 30 patients for an 8.3% (95%CI 5.4-11) cumulative incidence during the same follow-up period; seven major bleeding events were fatal (23%). Overall, 106 patients died, after a median follow-up of 48 days (interquartile range 6-80 days), for a cumulative incidence of 28% (95%CI 21-35). **Table 3** shows the univariate analysis of possible predictors of mortality, in which only metastatic cancer (OR 3.6; 95%CI 2.3-5.6) was significant. After multivariate analysis, metastatic cancer remained a significant predictor of mortality (adjusted OR 4.0; 95%CI 2.4-6.7).

Table 1. Baseline characteristics

		Study patients (n=372)
Age (y), mean ± st. dev		67 ± 13
Male sex, no. (%)		204 (55)
Previous use of anticoagulation therapy, no (%)		47 (13)[1]
Type of malignancy, no (%)	Cerebral	13 (3.5)
	Non-Hodgkin lymphoma	3 (0.80)
	Multiple myeloma	6 (1.6)
	Other hematologic malignancy	10 (2.7)
	Women genital tract	36 (9.7)
	Breast	55 (14.8)
	Testis	2 (0.50)
	Stomach	12 (3.2)
	Colon	32 (8.6)
	Other gastrointestinal	26 (7.0)
	Lung	60 (16)
	Other	103 (28)
	Unknown	14 (3.8)
Anaemia, no (%)		242 (65)[2]
Thrombocytopenia		80 (22)[3]
Impaired kidney function		49 (13)[4]
Presence of metastatic disease, no (%)		185 (50)[5]
Provoked VTE, no (%)		79 (21)[6]
Previous venous thromboembolism, no (%)		29 (7.8)

Note: st. dev=Standard deviation, VTE=Venous thromboembolism

Figure 2. Survival curve of LMWH discontinuation because of side effects in 372 patients.

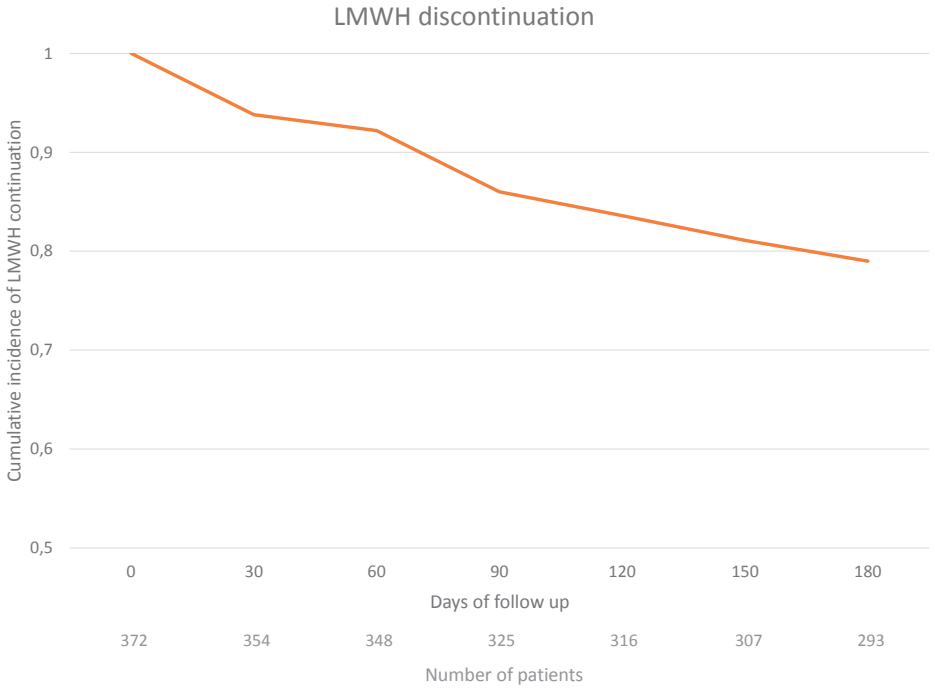


Table 2. Uni and multivariate analysis of predictors for LMWH discontinuation because of side effects in 372 patients

Predictor	Univariate RR (95%CI)	Multivariate RR (95%CI)
Age > 40 years	0.70 (0.28-1.7)	0.69 (0.25-1.9)
Female sex	1.61 (1.03-2.5)	1.7 (1.1-2.8)
Anaemia	0.89 (0.56-1.4)	1.2 (0.72-2.0)
Thrombocytopenia	1.0 (0.60-1.70)	1.1 (0.63-1.9)
Impaired kidney function	0.62 (0.29-1.4)	0.68 (0.30-1.5)
Hematologic cancer	0.41 (0.10-1.7)	1.1 (0.26-4.4)
Provoked VTE	1.0 (0.59-1.7)	0.99 (0.55-1.8)
Metastatic cancer	0.81 (0.52-1.3)	0.80 (0.49-1.3)
Previous use of anticoagulation therapy	0.89 (0.45-1.8)	0.95 (0.45-2.0)

Note: RR=Relative Risk, CI=Confidence Interval, VTE=Venous Thromboembolism

DISCUSSION

In this prospective observational study we found that one out of five patients with cancer-associated VTE discontinued LMWH injections because of side effects during a period of six months. The six-month cumulative incidence of discontinuation due to daily

Table 3. Uni and multivariate analysis of predictors for mortality in 372 patients during LMWH treatment

Predictor	Univariate RR (95%CI)	Multivariate RR (95%CI)
Age > 40 years	1.6 (0.52-5.2)	1.5 (0.36-6.1)
Female sex	0.85 (0.58-1.3)	0.83 (0.52-1.3)
Anaemia	1.6 (1.0-2.5)	1.4 (0.83-2.5)
Thrombocytopenia	0.64 (0.37-1.0)	0.75 (0.42-1.4)
Impaired kidney function	1.3 (0.79-2.3)	1.7 (0.96-3.2)
Hematologic cancer	0.65 (0.24-1.8)	1.2 (0.16-8.8)
Provoked VTE	0.74 (0.44-1.2)	0.65 (0.34-1.3)
Metastatic cancer	3.6 (2.3-5.6)	3.8 (2.2-6.4)
Previous use of anticoagulation therapy	1.2 (0.67-2.0)	0.94 (0.47-1.9)

Note: RR=Relative Risk, CI=Confidence Interval, VTE=Venous Thromboembolism

subcutaneous LMWH injections was 21%. This finding is consistent with other smaller and retrospective studies reporting similar percentages of patients who switched to oral anticoagulants within six months, although in these studies reasons for discontinuation were not provided (11, 13). Overall, half of the patients did not complete six months of LMWH treatment, which is also in line with previous studies (8-10). A remarkable finding was the fact that the most common reason for discontinuing LMWH treatment was pain at the injection site followed by injection site hematoma and allergic reactions. In this study, only female gender was found to be associated with discontinuation because of side effects.

When considering optimal management of patients with cancer-associated VTE, their overall prognosis and treatment preferences should be taken into account. The unfavorable prognosis of patients with cancer-associated VTE is clearly underlined by our study, reporting high cumulative incidences of mortality (28%), recurrent VTE (8.1%) and major bleeding (8.3%) until LMWH discontinuation, comparable with findings from previous landmark randomised trials after six months of follow up (4, 5). Importantly, although LMWH injection complications occurred in one of five patients, mirror wise four out five patients could continue. This may therefore be considered an acceptable trade-off against the reported higher risk of recurrent VTE associated with vitamin K antagonists (4-6). The recently introduced non-vitamin K dependent oral anticoagulants (DOACs) have the potential to be a valid alternative option for these patients, as these drugs share practical advantages with LMWH, are administered orally, and display a similar efficacy to VKAs but a lower bleeding risk in phase 3 studies in the general VTE population (18). The oral administration of DOACs might be more attractive and patient-friendly than daily subcutaneous LMWH injections. However, the performance of these agents has not sufficiently been investigated in patients with cancer-associated VTE, and a direct comparison is lacking (19). The results of our study provide a solid basis to

evaluate the use of DOACs in cancer-associated VTE. At present, the Hokusai VTE cancer study is randomizing patients with cancer-associated VTE to receive either dalteparin or edoxaban (20).

The strength of this study is the prospective multicenter set-up with a relatively large cohort of consecutive patients in daily practice, allowing for providing novel and clinically relevant data on the adherence and discontinuation due to complications of six months of daily subcutaneous LMWH administration in patients with cancer-associated VTE. We included a representative population given the fact that nearly 50% had metastatic disease and only 4.2% was lost to follow-up. Our study had limitations as well. We did not collect daily compliance to the LMWH therapy, and the impact of daily LMWH injections on quality of life was not evaluated.

To conclude, our study reveals that one out of five patients with cancer-associated VTE discontinued LMWH injections within six months because of side effects. The most common reasons for discontinuation were pain at the injection site, injection site hematoma and allergic reaction. Our findings provide important background information for current clinical trials investigating the efficacy and safety of DOACs compared to LMWH.

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Chapter 4

Higher adherence to treatment with LMWH nadroparin than enoxaparin for cancer related venous thromboembolism

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ABSTRACT

Introduction

Current guidelines recommend low-molecular-weight-heparins (LMWH) monotherapy for 3 to 6 months as first-line treatment for cancer-associated venous thromboembolism (VTE). In clinical practice enoxaparin and nadroparin are common agents used. However, differences in therapy adherence between these LMWHs have never been reported. Therefore, our aim was to compare adherence to enoxaparin and nadroparin in patients with cancer-associated VTE.

Materials and Methods

Consecutive patients with active cancer and objectively confirmed VTE, treated at a Dutch or a Spanish hospital, were followed during LMWH therapy with a maximum of 180 days. Cumulative incidences of discontinuation of both LMWHs were estimated and compared according to the Kaplan-Meier method, applying a competing risk analysis to correct for mortality.

Results

366 patients were analysed during LMWH treatment, of whom 284 patients (78%) were treated with enoxaparin and 82 (22%) with nadroparin. The cumulative incidence of discontinuation of enoxaparin and nadroparin treatment because of side effects was 30% (95%CI 24-36) and 8.8% (95%CI 1.1-15) respectively. Competing risk analysis revealed a higher number of patients discontinuing enoxaparin due to side effects (adjusted HR: 2.8; 95%CI 1.06-7.2). Pain at the injection site was the most common reason of discontinuation in patients using enoxaparin, occurring in 32 patients, while it occurred in one patient using nadroparin (adjusted HR: 4.0; 95%CI 0.52-31).

Conclusion

This analysis reveals that enoxaparin was associated with a higher risk of discontinuation because of side effects compared to nadroparin. However, given the nature of the patient groups, these findings should be followed by future studies.

INTRODUCTION

Low-molecular-weight heparins (LMWH) are recommended for at least three to six months as first-line treatment for cancer-associated venous thromboembolism (VTE) by most current international guidelines because of proven superior efficacy compared to conventional vitamin K antagonists (VKA), with comparable risk of major bleeding (1-3).

Recent research carried out at our institution has showed that one out of five patients with cancer-associated VTE stop LMWH injections because of side effects, mostly due to unacceptable pain at injection site (4). This finding was consistent with other smaller, retrospective studies reporting similar percentages of patients who switched to oral anticoagulants within six months (5, 6). These studies, however, did not distinguish between LMWH preparations.

In clinical practice, enoxaparin and nadroparin are commonly used LMWH agents for treatment of (cancer-associated) VTE. These different LMWHs are prepared by a variety of chemical and enzymatic depolymerisation techniques, resulting in marked differences in their physical and biochemical properties. These different characteristics might influence the burden of daily administration of subcutaneous injections. However, clinical data on the comparison of LMWHs is very limited and, so far, no single study has compared adherence to these LMWHs in patients with cancer-associated VTE. Two preliminary studies including heterogeneous patients have compared local tolerance of enoxaparin and nadroparin and suggested that the latter was locally better tolerated, possibly due to the difference in cationic salt composition (7, 8). Thus, more accurate detailed information about adherence to different LMWHs for the treatment of cancer-associated VTE is required.

The aim of the current study was to compare adherence to daily subcutaneous injections of enoxaparin and nadroparin in patients with cancer-associated VTE.

MATERIALS AND METHODS

Study population

This was a prospective, multi-centre, cohort follow-up study of consecutive patients with active cancer and objectively confirmed symptomatic proximal deep venous thrombosis (DVT) and/or pulmonary embolism (PE) to compare the adherence to enoxaparin and nadroparin during treatment with a maximum of 180 days. The design and characteristics of this cohort study have been described previously(4). However, in this study, only patients from the Leiden University Medical Centre (the Netherlands) and the Ramon Y Cajal hospital IRYCIS (Spain) with cancer-associated VTE between 2004 and 2014 and treated with therapeutic doses of LMWH were eligible for inclusion. In

these hospitals, two specific LMWH preparations were used; in Spain, all patients were treated with enoxaparin (enoxaparinum sodium 100mg (10,000 U/ml)) between 2004 and 2012 in the recommended dose of 1 mg/kg body weight twice daily (BID) in the first month, followed by as dosage of 1,5 mg/kg once daily (OD). In the Netherlands, all patients received weight-adjusted doses of subcutaneous nadroparin (nadroparinum calcium 9500 U/ml) between 2010 and 2014, either given once or twice daily - Fraxodi was given by 11,400 IU OD for patients under 70 kg and 15,200 IU OD for patients above 70 kg; Fraxiparine was given 5700 IU BID for patients under 70 kg and 7600 IU BID for patients 70 kg or more. At both hospitals, outpatient care comprised self-injections after standardized instructions by a trained nurse. All patients were followed during LMWH treatment with a maximum of 180 days and were excluded if they received other anticoagulants, were lost to follow up or experienced a venous catheter-associated thrombosis.

The institutional review board of both the Leiden University Medical Centre and the Ramon y Cajal Hospital IRYCIS approved the study and waived the need for informed consent due to its observational design.

Study endpoints

The primary objective of this study was to compare the discontinuation rate because of side effects of enoxaparin and nadroparin during the six-month study period. Reasons for discontinuation were determined by the treating physician during hospital visitation and categorized as follows: local side effects defined as hematomas at injection side, site pain and exanthema, and heparin induced thrombocytopenia. Patients were classified as having heparin-induced thrombocytopenia after a presumptive diagnosis, based on clinical parameters such as timing and degree of platelet count drop. The secondary objectives were to compare the incidences of recurrent VTE, major bleeding and mortality of both LMWHs.

Recurrent lower extremity DVT was defined as new non-compressibility by ultrasonography of the common femoral and/or popliteal vein for lower extremity DVT in the transverse plane or the vein diameter under maximum compression, as measured in the abnormal venous segment, showing enlargement of thrombus diameter (>4mm). Recurrent PE was defined as a new intraluminal filling defect on pulmonary angiography or CTPA, a new high probability perfusion defect on V/Q scan or any new defects after earlier normalization of the scan, or confirmation of a new PE at autopsy. V/Q-scans were evaluated according to the PIOPED criteria. Major bleed was defined in accordance with the International Society of Thrombosis and Haemostasis criteria(9). Cause of death was verified by reviewing the pathology report. If autopsy was not performed, the likely cause of death was verified with the treating physician by reviewing the medical records and death certificates. All secondary outcomes were adjudicated within the study group.

Statistical analyses

Means (standard deviation (SD)) and medians (interquartile range (IQR)) were used to present baseline continuous baseline variables for both LMWH groups. For categorical

Means (standard deviation (SD)) and medians (interquartile range (IQR)) were used to present baseline continuous baseline variables for both LMWH groups. For categorical variables, we used frequencies and percentages. The Pearson's Chi-square test was used to compare the distribution of the categorical variables, whereas the Mann-Whitney and independent t-test were used for non-normal and normal distributed continuous variables respectively. For analysis of primary and secondary endpoints, follow-up started at the moment of first LMWH administration and ended at time of LMWH discontinuation or the maximum follow-up period of 180 days. The cumulative incidence of discontinuation of both LMWHs, recurrence VTE and bleeding events were estimated according to the Kaplan-Meier method, presented with two-sided 95% confidence intervals (CI). A comparison was then made by a Cox-proportional hazard model, adjusted for gender, age, impaired kidney function and metastatic cancer, applying a competing risk analysis in which a patient was either censored for a specified outcome or not, and in the latter case completed the entire follow up period (demonstrated with a Hazard Ratio (HR))(10). Data were analysed using SPSS version 23 (SPSS inc., Chicago IL). A p-value below 0.05 was considered significant.

RESULTS

Study population

A total of 366 patients were analysed during LMWH treatment, of whom 284 patients (78%) were treated with enoxaparin and 82 (22%) with nadroparin (67 patients (82%) with Fraxodi OD and 15 (18%) with Fraxiparin BID). **Table 1** shows the baseline characteristics of both LMWH therapies. Patients receiving enoxaparin were significantly older (mean age 68 years (SD 12) vs. 62 years (SD 13)). Impaired kidney function and metastatic cancer were more present in patients treated with nadroparin (27% vs. 9.7% and 63% vs. 45% respectively).

Discontinuation of LMWH treatment

Overall, 192 patients (52%) discontinued LMWH treatment within six months, of whom 151 patients (53%) were treated with enoxaparin and 41 patients (50%) with nadroparin. Reasons for discontinuation are shown in **Table 2.** A total of 77 patients (21%) discontinued LMWH treatment because of side effects; of whom 71 patients (92%) stopped enoxaparin after a median duration of 90 days (IQR 30-90 days) and six patients (7.8%) nadroparin after a median duration of 66 days (IQR 19-125 days; five patients using

Table 1. Baseline characteristics

		Nadroparin (n=82)	Enoxaparin (n=284)
Age (y), mean ± st. dev		62 ± 12	68 ± 13*
Male sex, no. (%)		51 (62)	152 (54)
Previous use of anticoagulation therapy, no (%)		16 (20)	31 (11)*
Type of malignancy, no (%)	Cerebral	3 (3.7)	10 (3.5)
	Non-Hodgkin lymphoma	2 (2.4)	1 (0.40)
	Multiple myeloma	4 (4.9)	2 (0.70)*
	Other haematologic malignancy	6 (7.3)	4 (1.4)*
	Women genital tract	15 (18)	19 (6.7)*
	Breast	4 (4.9)	49 (17)*
	Testis	1 (1.2)	1 (0.40)
	Stomach	2 (2.4)	10 (3.5)
	Colon	3 (3.7)	29 (10)
	Other gastrointestinal	12 (15)	14 (4.9)*
	Lung	14 (17)	46 (16)
	Other	16 (20)	85 (30)
	Unknown	0	14 (15)*
Anaemia, no (%)		53 (65)	188 (66)
Thrombocytopenia, no (%)		17 (21)	63 (22)
Impaired kidney function, no (%)		22 (27)	27 (9.7)*
Presence of metastatic disease, no (%)		52 (63)	127 (45)*
Immobilisation in the past four weeks, no (%)		21 (26)	28 (9.9) *
Previous venous thromboembolism, no (%)		7 (8.5)	21 (7.4)

Note: st. dev=Standard deviation

Table 2. Reasons for LMWH discontinuation

Reason, no (%)	**Nadroparin (n=82)**	**Enoxaparin (n=284)**
Recurrent VTE	1 (1.2)	18 (6.3)
Bleeding	3 (3.6)	8 (2.9)
Death*	27 (33)	52 (18)
Curation of cancer	1 (1.2)	2 (0.7)
LMWH side effects	6 (7.3)	71 (25)
Other	2 (2.4)	0
Unknown	1 (1.2)	0
Total	41 (50)	151 (53)

Note: VTE=Venous Thromboembolism

fraxodi OD, one patient using fraxiparin BID). The Kaplan Meier survival for discontinuation of both LMWHs because of side effects is shown in **Figure 1**. The overall cumulative incidence of discontinuation during six months of enoxaparin and nadroparin treatment was 30% (95%CI 24-36) and 8.8% (95%CI 1.1-15) respectively. Competing risk analysis revealed a significant higher number of patients discontinuing enoxaparin (adjusted HR: 2.8; 95%CI 1.06-7.2).

Figure 1. Discontinuation of both LMWHs because of side effects after a maximum follow up period of 180 days

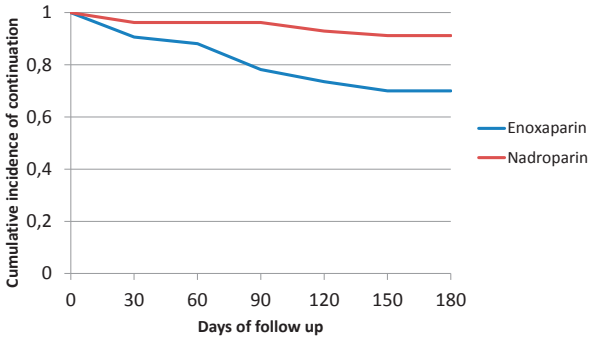

Table 3 shows LMWH side effects that led to discontinuation. Interestingly, pain at the injection site was the most common reason of discontinuation in patients using enoxaparin, occurring in 32 patients (cumulative incidence: 15% (95%CI 10-19)), while it occurred in one patient using nadroparin (cumulative incidence: 1.7% (95%CI 0-5.0);adjusted HR: 4.0; 95%CI 0.52-31). Discontinuation because of local exanthema only occurred in 15 patients who were treated with enoxaparin (cumulative incidence: 7.1% (95%CI 3.6-11).

Table 3. Reasons for LMWH discontinuation because of side effects

Reason, no (%)	**Nadroparin (n=82)**	**Enoxaparin (n=284)**
Heparin induced thrombocytopenia	2 (2.4)	1 (0.035)
Hematoma at injection site	3 (3.7)	23 (8.1)
Local exanthema	0	15 (5.3)
Pain	1 (1.2)	32 (11)

Recurrent VTE, bleeding and mortality

During the six month study period, a recurrent VTE occurred in 23 patients treated with enoxaparin after a median duration of 60 days (IQR 27-120 days) and in six patients treated with nadroparin after a median duration of 118 days (IQR 34-180 days), for a respective cumulative incidence of 11% (95%CI 6.4-15) and 7.6% (95%CI 1.8-13; adjusted HR: 2.9; 95%CI 0.65-13). Major bleeding events occurred in 27 patients using enoxaparin

after a median duration of 90 days (IQR 30-120 days) and in two patients using nadroparin after a median duration of 66 days (IQR 34-66 days), for a respective 11% (95%CI 6.9-15) and 2.7% (95%CI 0-6.4) cumulative incidence (adjusted HR: 5.1; 95%CI 0.66-39).

Seventy-one patients died during enoxaparin treatment after a median duration of 60 days (IQR 30-90 days) and 30 patients died during nadroparin treatment after a median duration of 77 days (IQR 30-140), for a respective cumulative incidence of 29% (95%CI 23-34) and 39% (95%CI 29-49; adjusted HR: 1.3; 95%CI 0.76-2.3).

DISCUSSION

Our main observation was a significantly higher risk of discontinuation of LMWH treatment because of side effects of enoxaparin than of nadroparin in patients with cancer-associated VTE. During the six-month study period, the adjusted hazard ratio of discontinuation because of side effects of enoxaparin was 2.8 compared to nadroparin treatment. These results elaborate on the findings of our previous study demonstrating a cumulative incidence of one out of five patients discontinuing both LMWHs due to side effects (4). The observed 30% cumulative incidence of discontinuation of enoxaparin was substantially higher than described in a previous study, reporting an incidence of 14% in a very small number of younger cancer patients treated with a similar dose (11). In comparison, the observed 8.8% cumulative incidence of discontinuation of nadroparin was consistent with those of a previous report, studying only patients with metastatic or locally advanced solid cancer (12).

Pain at the injection site was the most common reason of discontinuation in patients using enoxaparin (45%), while occurring in only one patient using nadroparin (14%). This finding is in line with previous studies reporting a higher incidence of pain at the injection site in patients using enoxaparin than in patients using nadroparin, although these studies deal with different patient groups and a relatively short study period (7, 8). They suggested that the pain intensity increased with the sodium concentration in enoxaparin, while in contrast, nadroparin is salified with calcium. Regarding pharmacodynamics and kinetics, only slight differences exist between both LMWHs (13-15). Thus, the sodium concentration in enoxaparin might be responsible for increased pain at the injection site, thereby leading to early discontinuation. However, since the proportion of salt dissolved in the LMWH preparations is almost negligible and other licensed LMWHs for the treatment of cancer-associated VTE (i.e. tinzaparin and dalteparin) also contain sodium, this hypothesis seems unlikely. Unfortunately, no data were available on needle size differences of both LMWHs, which could also have contributed to our findings. A former study, however, found no reduction of pain and hematoma size in patients with cardiovascular disease using enoxaparin with two different needle gauges (16). Discon-

tinuation because of local exanthema only occurred in 15 patients using enoxaparin (cumulative incidence: 7.1%). This finding differs from a previous prospective study demonstrating a higher incidence proportion of heparin-induced skin lesions in patients treated with nadroparin (17%) than enoxaparin (3.9%) in 321 patients who used LMWH for a minimum of seven days (17). However, from all these reports, it is unclear whether the occurrence of side effects was a reason for discontinuation of therapy.

Comparative studies have not been performed to determine whether one LMWH is superior over the other in the treatment of cancer-associated VTE. In this study we found similar incidences of recurrent VTE and bleeding events of both LMWH agents.

This study has strengths and limitations. We included a large cohort providing novel and clinically relevant data on adherence to two different commonly used LMWH therapies in cancer-associated VTE. The most important limitation of this study was the non-randomised design. Both LMWHs were allocated according to the policy of the treating hospital and availability in the regional Dutch and Spanish pharmacies, thereby leading to differences in patient characteristics. Moreover, the evaluation of primary outcomes were not standardized, as treating physicians were only requested to report the reason of discontinuation and a HIT diagnosis was based on clinical assumption. For practical reasons, we combined two prospective databases (e.g. Spanish and Dutch cohorts) with a different time frame of inclusion. We do not believe this would have influenced the discontinuation rate. During the ten-year inclusion period of enoxaparin, possible changes in composition or preparation techniques did not lead to different discontinuation rates. However, because of different inclusion durations, patients were not equally distributed among both groups. Additionally, in our adjusted analyses, it was not possible to correct for all potential confounders. Other characteristics such as social economic status and health coverage might also have influenced these findings. Furthermore, all Spanish patients were treated with enoxaparin injections BID for the first month, which could have led to a higher discontinuation rate. However, discontinuation of enoxaparin occurred only in 25% of the patients during the first month of BID administration. In comparison, of the 18% BID using nadroparin patients, only one discontinued during the six month treatment period. Hence, this was presumably of minor influence. Lastly, given the occurrence of relatively small number of individual reasons for discontinuation, our study did not achieve adequate power to detect possible significant differences between side effects of these two LMWHs.

In conclusion, our study reveals a significantly higher risk of discontinuation because of side effects of enoxaparin than nadroparin treatment in patients with cancer-associated VTE. However, these findings should be interpreted with caution owing to inherent patient groups, and more studies are needed to corroborate our findings.

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Part 2

Arterial thrombotic complications after heart valve surgery

Chapter 5

Antithrombotic strategy after bioprosthetic aortic valve replacement in patients in sinus rhythm: evaluation of guideline implementation

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ABSTRACT

Objectives

After elective aortic valve replacement patients are at risk of developing valve thrombosis and systemic arterial thromboembolism. Current guidelines recommend antithrombotic therapy with aspirin or vitamin K antagonists (VKA) during the first three months after the procedure but have level 2 or 3 evidence. As a consequence, the most appropriate antithrombotic therapy is still a matter of debate. This retrospective study analysed all thromboembolic and bleeding complications in patients with either antiplatelet or anticoagulation therapy one year after bioprosthetic aortic valve replacement.

Methods

A total of 402 patients undergoing bioprosthetic aortic valve implantation at the VU University Medical Centre (VUmc) and subsequently treated at three regional hospitals were included. The individual duration of either vitamin K antagonists (acenocoumarol) or aspirin was determined and related to thrombotic and bleeding events. Patients were followed and censored at 1 year postoperatively for survival, cerebral ischemia, myocardial infarction, peripheral arterial embolism and minor and major haemorrhages.

Results

A total of 24 thromboembolic complications and 31 bleeding episodes occurred. Multivariable analyses revealed that acenocoumarol caused more bleedings (relative risk (RR): 8.41, 95%CI: 3,58-19.79) and a similar amount of thromboembolic events (RR: 1.2, 95% CI: 0.47-3.02) compared to aspirin. Prior use of acenocoumarol was found to be a risk factor for thromboembolic events (RR: 3.1, 95% CI: 1.31 to 7.19). Gender, dyslipidemia, prior percutaneous coronary intervention, prior use of acenocoumarol and concomitant coronary artery bypass grafting were found to be predictors for bleeding events.

Conclusions

In patients one year following bioprosthetic aortic valve replacement, acenocoumarol therapy was associated with a significant increased risk in bleeding events and no reduction of thromboembolic events compared to antiplatelet therapy. These findings support the recommendations of aspirin over VKA as post-operative thromboprophylaxis one year postoperatively.

INTRODUCTION

Patients undergoing artificial heart valve replacement are at risk of developing valve thrombosis and systemic thromboembolism. The annual risk of thromboembolic events in patients with a mechanical aortic valve is 1-2% versus 0.7% with a bioprosthetic aortic valve, even with appropriate antithrombotic therapy (1). The need for lifelong anticoagulant therapy is well established in all patients with mechanical heart valves. In patients with bioprosthetic aortic valves anticoagulant therapy is warranted in the presence of thromboembolic risk factors including atrial fibrillation, previous thromboembolism, left ventricular dysfunction and hypercoagulable condition. In patients without one of these risk factors, the appropriate antithrombotic regimen postoperatively is still a matter of debate.

Recommendations of current guidelines are shown in **Table 1** (1-4). Although based on small or retrospective studies without conclusive results, there is a trend towards the recommendation of aspirin after implantation of a bioprosthetic aortic valve (2, 5-10). Therefore, after the 1st of July 2011, the antithrombotic policy in the VU University medical centre (VUmc) was changed and patients with sinus rhythm did no longer receive VKA.

Earlier studies demonstrated that, despite guidelines published by several professional societies, medical practice for the prevention of thrombotic events early after bioprosthetic aortic valve replacement varies widely among cardiac surgical centres (11-14). Thus, despite recommendations, there is still disparity of opinions in clinical practice.

Table 1. Current recommendations for antithrombotic strategy after bioprosthetic aortic valve replacement in patients who are in regular sinus rhythm and have other indications for VKA therapy (1-4).

Organization, year	Recommendation	Grade of evidence
ESC, 2012	Low-dose aspirin should be considered for the first three months after implantation of an aortic bioprosthesis	2C
ACC/AHA,2014	Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic valve. Anticoagulation, with a VKA, to achieve an INR of 2.5 may also be reasonable for the first 3 months after bioprosthetic AVR	2B
ACCP, 2012	In patients with aortic bioprosthetic valves we suggest aspirin (50-100 mg/d) over VKA therapy in the first 3 months	2C
EACTS, 2008	After tissue aortic valve replacement anticoagulation therapy is reasonably safe and may be beneficial. Antiplatelet therapy alone however is an acceptable alternative	2B

Note: ESC = European Society of Cardiology, ACC= American College of Cardiology, AHA= American Heart Association, ACCP= American College of Chest Physicians, EACTS= European Association for Cardio-Thoracic Surgery, VKA= Vitamin K Antagonists.

In summary, antithrombotic management after bioprosthetic aortic valve replacement is still a matter of debate. Therefore, the purpose of this study was to analyse thromboembolic events and bleeding complications in patients with either antiplatelet or anticoagulation therapy one year following bioprosthetic aortic valve surgery. For this purpose, different antithrombotic regimens before and after 2011 were compared. In addition, individual duration of either vitamin K antagonists or aspirin was related to thrombotic and bleeding events.

MATERIALS AND METHODS

The local Human Subjects Committee of the VU University Medical Centre approved this retrospective evaluation and waived the requirement to obtain informed consent.

This was an observational retrospective study of consecutive patients who underwent an isolated bioprosthetic aortic valve replacement to measure postoperative outcomes. Data were collected from the prospective database of the department of cardiothoracic surgery of the VUmc. Patients had undergone isolated aortic valve replacement between 2008 and 2014 and had been subsequently seen in three regional hospitals. In all three hospitals postoperative medical files were obtained and evaluated. Additionally, the thrombosis service was consulted about the duration of the treatment, the international normalized ratios (INRs), and target values of patients who received the vitamin K antagonist drug acenocoumarol. Except for patients undergoing concomitant bypass surgery, all other patients with concomitant procedures were excluded. Thromboembolic events and bleeding complications that occurred at the first postoperative day were not taken into consideration because antithrombotic treatment was started only at this day.

All patients were operated at the department of cardiac surgery at the VUmc and received an aortic bovine pericardial bioprosthesis (type, Carpentier-Edwards PERIMOUNT, Edwards Lifesciences, USA). Low-molecular-weight heparin (LMWH) nadroparin 2850 IU/day, or 2850 IU twice a day if a patient's weight was above 100 kg, was started on the first postoperative day followed by acenocoumarol or aspirin. Nadroparin was continued until acenocoumarol reached therapeutic levels, as shown by a prothrombin time (PT) according to the international normalized ratio (INR) (range, 2.5 to 3.5 according to the Dutch Thrombosis Service guidelines) or as soon as the patient was ambulant when patients received aspirin. Anticoagulation with acenocoumarol was maintained for three postoperative months, then discontinued at the discretion of the referring cardiologist and most often replaced by aspirin. Those with concomitant coronary artery bypass grafting did not receive double antithrombotic therapy (warfarin plus aspirin) but received aspirin only. After 1st of July 2011, a new treatment regimen was installed in the VUmc and patients no longer received standard VKA treatment bridged by LMWH.

The policy was changed because of lack of scientific evidence for indication of VKA and also anecdotal reporting of post-operative complications due to VKA therapy, especially early tamponade (2). From then on, aspirin (100mg per day) was started on the first postoperative day and continued lifelong in patients with sinus rhythm (see **table 2** regimes). Aspirin therapy could be changed to VKA therapy if thrombotic risk factors such as atrial fibrillation and thromboembolism were present.

Table 2. Post-operative antithrombotic strategies of different regional hospitals after bioprosthetic aortic valve replacement, in the absence of risk factors. *Change of policy was at the 1st of July 2011*

	Antithrombotic Strategy	
Regional hospital	**Before change of policy**	**After change of policy**
MCA	three months acenocoumarol substituted with life-long aspirin	life-long aspirin
ZMC	three months acenocoumarol substituted with life-long aspirin if concomitant coronary artery disease	life-long aspirin
KG	three months acenocoumarol substituted with life-long aspirin	life-long aspirin

Note: MCA = Medical Centre of Alkmaar, ZMC = Zaans Medical Centre, KG = Kennemer Gasthuis

To establish the exact period of the administration of acenocoumarol within a year, the thrombosis service was consulted. The exact period of aspirin use was assumed to be according to the prescription of the treating physician without interruption. Patients were followed and censored at one-year for administrative reasons and were observed on occurence of death, cerebral ischemia, including cerebrovascular accidents (CVAs) and transient ischemic attacks (TIAs), peripheral embolisms, myocardial infarction and minor and major bleeding. All thromboembolic events were defined according to the guideline reported by Edmunds *et al.* (15). Bleeding was defined as major if overt and associated with a decrease in hemoglobin level of 2 g per decilitre or more, required the transfusion of 2 or more units of blood, occurred into a critical site – i.e. intracerebral, intra-ocular, intraspinal, or intra-articular, or contributed to death. Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, contact with a physician, interruption of antithrombotic treatment, or discomfort or impairment in carrying out activities of daily life. These events were examined in relation to the antithrombotic therapy and in relation to potential predictive risk factors such as gender, age, diabetes, hypertension, dyslipidemia, a history of smoking, prior embolism, prior cardiac surgery and prior use of antithrombotic therapy. Risk factors were defined according to the documentation provided by the treating physician.

Statistics

Baseline characteristics were stratified according to patients who underwent surgery before and after policy change of the VUmc in 2011. The Pearson's Chi-square test was used to compare the distribution of categorical variables, whereas the Mann-Whitney and independent *t*-tests were used for non-normal and normal distributed continuous variables respectively. Purely for descriptive purposes for thromboembolic and bleeding events we calculated Kaplan-Meier curves over a year. Patients were censored at date of last medical chart documentation or after loss to follow-up.

Risk (Rate) Ratios (RRs) for the occurrence of thromboembolic and bleeding events on the cumulative number of days of antithrombotic therapy of one antithrombotic therapy versus the other were estimated with Poisson regression using generalized estimating equations (GEE). To assess the influence of independent predictive risk factors on thromboembolic and bleeding events a multivariable Poisson regression was performed using all potential risk factors simultaneously which in univariable Poisson regressions had a p-value lower than 0.15 and those of clinical importance. All analyses were performed using SPSS version 21.

RESULTS

In total 402 patients were included (mean age 75 years, 56.2% men). **Table 3** shows an overview of baseline characteristics. The individual duration of either acenocoumarol or aspirin use could be assessed in 384 patients and related to the number of thromboembolic and bleeding events. In 22 patients data on the exact number of days of medication use were not complete, because detailed information of potential therapy changes could not be retrieved from medical files. As expected, the cumulative number of days of aspirin use was less before than after the adjustment of treatment policy. A total of 51 patients experienced an event; 20 patients had a thromboembolic event and 26 patients had a bleeding episode. In four patients both a thromboembolic and a bleeding event occurred. One patient had two minor bleeding events. The number of events before and after 2011 did not differ significantly (bleeding events: p= 0.35, thromboembolic events: p=0.59).

Table 4 lists the sites of bleeding and thromboembolic events and the treatment regimen. Of 31 bleeding events, 14 were major bleedings. Most bleedings were gastrointestinal (42%) of which one was fatal. In total, 81% of the bleeding events occurred during treatment with acenocoumarol. Most of the thromboembolic events were transient ischemic attacks (41%). The patient who experienced a myocardial infarction received both aspirin and acenocoumarol. The occurrence of thromboembolic events was similar for both acenocoumarol and aspirin.

Table 3. Baseline characteristics

Characteristic		total (n=402)	before change of policy (n=163)	after change of policy (n=239)
Age (y), mean ± st. dev		74,9 ± 6,9	76,0 ± 6,6	74,2 ± 7,1
Gender	male	226 (56,2)	86 (52,8)	140 (58,6)
	female	176 (43,7)	77 (47,2)	99 (41,4)
logEuroscore, mean ± st. dev		7,3 ± 5,1	8,3 ± 5,7	6,5 ± 4,5*
	missing, no.	19		19
Prior CVA, , no (%)		29 (7,2)	11 (6,7)	18 (7,5)
Prior MI, no (%)		37 (9,2)	9 (5,5)	28 (11,7)*
Prior embolism, no (%)		42 (10,4)	19 (11,7)	23 (9,6)
LV function, no (%)	>40%	355 (88,3)	146 (89,6)	209 (87,4)
	20-40%	32 (8,0)	12 (7,4)	20 (8,4)
	<20%	14 (3,5)	5 (3,1)	9 (3,8)
	missing	1 (0,2)	0	1 (0,4)
Preoperative AF, no. (%)		51 (12,7)	22 (13,5)	29 (12,1)
	missing	31 (7,7)	7 (4,3)	24 (10)
Dyslipidemia, no. (%)		130 (32,3)	48 (29,4)	82 (34,3)
	missing	1 (0,2)	1 (0,6)	
Previous CABG, no. (%)		14 (3,5)	5 (3,1)	9 (3,8)
Previous PCI, no. (%)		44 (10,9)	13 (8,0)	31 (13,0)
Smoking, no. (%)		75 (18,7)	30 (18,4)	45 (18,8)
Preoperative aspirin, no. (%)		178 (44,3)	81 (49,7)	96 (40,2)
Previous acenocoumarol, no. (%)		59 (14,7)	17 (10,4)	43 (18,0)*
Aortic disease, no. (%)	stenosis	353 (87,7)	143 (87,7)	210 (87,9)
	regurgitation	21 (5,2)	8 (4,9)	13 (5,4)
	mixed	27 (7,6)	11 (6,7)	16 (6,7)
	missing	1 (0,2)	1 (0,6)	0
Concomitant CABG, no. (%)		169 (42)	73 (44,8)	96 (40,2)
	missing, no.	2	2	0
Repeat thoracotomy, no (%)		25 (6,2)	17 (10,4)	8 (3,3)*
	missing	31 (7,7)	0	31 (13,0)
Sum of days of therapy use, days (median)	Aspirin	67725 (202)	22028 (162)	46062 (242)*
	Acenocoumarol	56469 (112,5)	30482 (154)	25987 (0)*
	missing, no.	18	12	6
Number of bleeding events, no. (%)		32 (8,0)	16 (9,8)	16 (6,7)
Number of thromboembolic events, no. (%)		24 (6,0)	11 (6,7)	13 (5,4)

Note: y=years, st. dev.=Standard Deviation, CVA=Cerebrovascular Accident, MI=Myocardial Infarction, LV=Left-ventricular, AF=Atrial Fibrillation, CABG=Coronary Artery Bypass Graft, PCI=Percutaneous Coronary Intervention

Table 4. Bleeding and thromboembolic events

			Antithrombotic therapy		
		No. Events	Acenocoumarol	Aspirin	Neither
Bleeding events		32	26 (81%)	6 (19%)	0
Site of events, no. (%)					
	Cerebral	2 (6%)	2 (100%)	0	0
	Gastrointestinal	14 (44%)	11 (79%)	3 (21%)	0
	Urinary	7 (22%)	5 (83%)	1 (17%)	0
	Epistaxis	4 (13%)	3 (75%)	1 (25%)	0
	Other	5 (16%)	4 (80%)	1 (20%)	0
TE events		24*	12 (52%)	11 (45%)	2 (8%)
Site of events, no. (%)					
	CVA	7 (32%)	3 (43%)	4 (57%)	0
	TIA	9 (41%)	6 (67%)	2 (22%)	1 (11%)
	Myocardial infarction	1 (4,5%)	1 (50%)	1 (50%)	0
	Pulmonary embolism	1 (4,5%)	0	1 (100%)	0
	Deep vein thrombosis	2 (9%)	0	1 (50%)	1 (50%)
	other	4 (18%)	2 (50%)	2 (50%)	0

Note: CVA = Cerebrovascular Accident, TIA = Transient Ischemic Attack

Univariable analysis of risk factors on events is shown in **Table 5**. There was a highly increased risk in the incidence of bleeding events when using acenocoumarol after one year of follow-up compared to aspirin (RR: 18.32, 95% CI: 5,41 to 62,07). In addition, seven other risk factors were predictive for bleedings: gender (p=0.001), age (p<0.001), prior percutaneous coronary intervention (p<0.001), hypertension (p=0.004), dyslipidemia (p<0.001) and concomitant coronary artery bypass grafting (p<0.001). In multivariable analysis the incidence of bleeding events remained significantly higher in patients using acenocoumarol compared to patients with aspirin use (RR: 8.41, 95%CI: 3.58 to 19.79). Gender, prior percutaneous coronary intervention, dyslipidemia, prior use of acenocoumarol and concomitant coronary artery bypass grafting remained all independent predictors for bleeding events (**Table 6**). Also for *major* bleedings acenocoumarol remained a predictor in univariable and multivariable analyses (multivariable: RR: 14.60, 95%CI: 1.95 to 109.37). For thromboembolic events, both in uni- and multivariable analysis, there was no significant difference one year postoperatively when using acenocoumarol or aspirin (multivariable RR: 1.2, 95% CI: 0.47-3.02). Only prior use of acenocoumarol appeared to be an independent predictor of thromboembolic events both in uni- and multivariable analysis (p=0.007).

Kaplan Meier survival curves for the first episode of any event, including mortality, are shown in **figure 1**. 50% of the bleeding and 63% of the thromboembolic complications occurred within 3 months. Comparing the events before and after policy change in

Table 5. Univariable analysis of risk factors on bleeding and thromboembolic events in 384 patients (unless specified otherwise) one year after bioprosthetic aortic valve replacement.

	Bleeding events			TE events		
Variable	RR	95%CL	P-value	RR	95%CL	P-value
Acenocoumarol	18,32	5,41-62,07	<0,001	1,11	0,44-2,77	0,83
Male	0,15	0,05-0,46	0,001	0,815	0,36-1,85	0,62
Age	1,07	1,04-1,11	<0,001	1,01	0,95-1,07	0,8
LogEuroscore (n=365)	1,04	0,98-1,12	0,21	0,99	0,93-1,07	0,97
Prior CVA	2,01	0,64-6,36	0,23	1,2	0,30-4,92	0,79
Prior CABG	0,24	0,03-2,17	0,2	1,37	0,20-9,39	1,75
Prior PCI	32,09	17,26-59,66	<0,001	0,8	0,20-3,31	0,76
Prior embolism	0,31	0,06-1,58	0,16	0,87	0,21-3,56	0,84
Diabetes	1,5	0,74-3,04	0,26	1,43	0,58-3,54	0,44
Smoking	0,34	0,08-1,36	0,13	1,34	0,51-3,52	0,55
Hypertension	6,2	1,82-21,3	0,004	1,47	0,60-3,59	0,4
Dyslipidemia (n=383)	4,74	3,00-7,48	<0,001	1,27	0,54-2,96	0,58
Repeat thoracotomy (n=354)	0,54	0,08-3,75	0,53	0,85	0,12-5,60	0,87
Prior ASA (n=381)	1,47	0,77-2,78	0,24	0,72	0,30-1,70	0,45
Prior Acenocoumarol (n=381)	0,27	0,5-1,35	0,11	3,06	1,31-7,19	0,01
History of AF (n=351)	0,65	0,20-2,07	0,46	1,55	0,52-4,57	0,43
Concomitant CABG	2,83	2,13-3,76	<0,001	1,55	0,68-3,52	0,3
Before policy change	0,54	0,21-1,39	0,21	0,79	0,26-2,39	0,67

Note: TE = thromboembolic, RR=Relative Risk, CI=Confidence Interval, MI= Myocardial infarction, CVA = Cerebrovascular Accident, CABG= Coronary Artery Bypass Grafting, PCI=Percutaneous Coronary Intervention, AF= Atrial Fibrillation

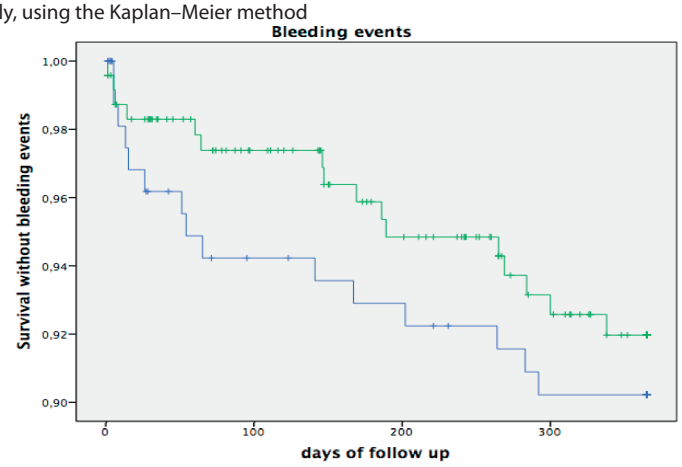
Table 6. Multivariable Poisson regression with selected independent predictors that had p-values below 0.15 and were of clinical importance in 384 patients (unless specified otherwise) after bioprosthetic aortic valve replacement.

	Bleeding			TE events		
Predictor	RR	95%CI	P-value	RR	95%CI	P-value
Acenocoumarol	8,41	0,36-19,79	<0,001	1,2	0,47-3,02	0,7
Male	0,14	0,36-1,62	<0,001	0,82	0,36-1,89	0,65
Age	1,02	0,96-1,08	0,49	1,01	0,95-1,07	0,77
Prior MI	0,35	0,07-1,69	0,19	-	-	-
Prior PCI	10,75	5,54-20,88	<0,001			
Smoking	1,6	0,65-3,95	0,31	-	-	-
Hypertension	1,82	0,80-4,16	0,16	-	-	-
Dyslipidemia (n=383)	2,29	1,26-4,19	0,007	-	-	-
Prior Acenocoumarol (n=381)	2,46	1,32-4,56	0,004	3,1	1,37-7,4	0,007
Concomitant CABG	3,32	1,70-6,48	<0,001	-	-	-

Note: TE = thromboembolic, RR=Relative Risk, CI=Confidence Interval, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass surgery.

Figure 1. Survival to bleeding (A), thromboembolic events (B) and overall survival (C) in 402 patients 1 year postoperatively, using the Kaplan–Meier method

A.



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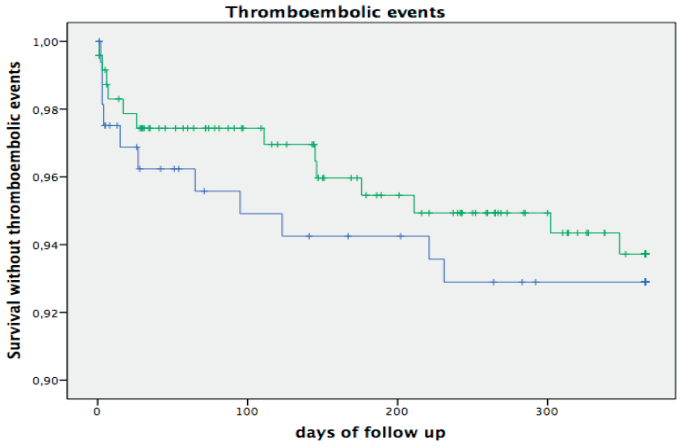
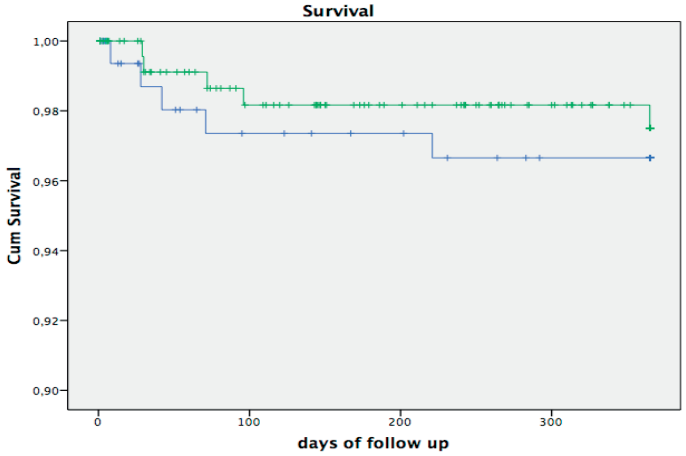


C.



Blue = before policy change 2011, green = after policy change 2011.

2011, no significant difference in event-free survival could be demonstrated (bleeding: p=0.48, thromboembolism: p=0.83, mortality: p=0.58), possibly due to the larger number of patients using acenocoumarol preoperatively, which is a predictor for bleeding, after policy change in 2011. During one year follow-up 10 patients (2%) died, of who four died before the antithrombotic policy change at the VUmc. Approximately 50% of all events occurred within 100 days after aortic valve implantation. Causes of death were sepsis (three patients), cardiac arrest, gastrointestinal bleeding, aortic dissection, respiratory failure and post-anoxic encephalopathy. In one patient, the cause of death was unknown.

DISCUSSION

The main finding of this study was a significantly increased incidence of minor and major bleeding events without a reduction of thromboembolic events during acenocoumarol therapy compared to aspirin use one year after bioprosthetic aortic valve replacement.

Our study reinforces the recommendations of the ACC/AHA, ACCP, ESC and the EACTS guidelines suggesting antiplatelet therapy as adequate or acceptable thromboprophylaxis. These recommendations have been revisited in the last decade after more recent publications about the absence of a beneficial effect of warfarin (1-4). Five studies have compared antiplatelet with anticoagulation therapy in patients with bioprosthetic aortic valves (**Table 7**) (5-7, 16, 17). Four of them found no advantages in performing early anticoagulation therapy compared with a low-antiplatelet regimen. Colli *et al.* (2013) demonstrated higher morbidity in patients using VKA after bioprosthetic aortic valve replacement. Other recent studies comparing early to no anticoagulation have reported no significant difference in bleeding episodes and no reduction in thromboembolism (9, 18). Elbardassi *et al.* and Jamieson *et al.* even suggested that early antithrombotic therapy had no beneficial effect in patients without risk factors (19, 20). As a result, since most studies have been either retrospective or underpowered, the thrombotic prophylaxis after bioprosthetic aortic valve replacement remains controversial. The treatment policy of the VUmc, based on current guidelines, was changed in 2011 and now advises the use of aspirin instead of VKA in patients without risk factors (2).

In contrast to the findings by Goldsmith *et al*., age, hypertension, diabetes, dyslipidemia, a history of smoking and left ventricular function were no predictors of postoperative thromboembolic events (21). In our study only prior use of acenocoumarol was found to be a predictive risk factor for thromboembolic events. Those who received acenocoumarol before operation may have been more sensitive to thromboembolism by other risk factors, mostly atrial fibrillation.

Table 7. Summary of findings: Antiplatelet versus anticoagulation therapy after bioprosthetic aortic valve replacement (5-7, 16, 17)

Author, year	Study design, follow up	Conclusion
Blair *et al.* 1994	Retrospective, 3 months	No significant differences
Gherli *et al.* 2004	Prospective observational, 3 months	No significant differences
Aramendi *et al.* 2005	Prospective, 6 months	No significant differences
Colli *et al.* 2007	Prospective, 3 months	No significant differences
Colli *et al.* 2013	Prospective, 6 months	Higher morbidity within 6 months using VKA

Note: VKA= vitamin K antagonists

Most studies have found no significant differences in thromboembolic events or bleeding complications between patients treated with anticoagulation therapy and patients treated with an antiplatelet regimen, whereas our study demonstrated that antiplatelet therapy has an apparent safety benefit in the first year after bioprosthetic aortic valve replacement and that this does not come with an increased thromboembolic risk. Still, in this uncontrolled setting, there could have been unknown risk factors that may have influenced these results. Nevertheless, our results indicate that aspirin should be considered the preferred antithrombotic regimen compared to acenocoumarol. This is in line with the recommendations of aspirin use after bioprosthetic aortic valve replacement by the AHA/ACC, ACCP, ESC and EACTS guidelines. Moreover, we think that our findings suggest that AHA/ACC and EACTS should revisit the recommendation of vitamin K antagonists as an acceptable alternative. This recommendation of the ACC/AHA guidelines is based on a recent retrospective study that demonstrated a clear benefit associated with warfarin versus no warfarin during the initial three months after surgery (8). These findings, however, are based on different study populations. In our study two more homogenous groups could be compared. The beneficial effect of aspirin compared to no treatment at all cannot be answered from the results of our study.

Strength of our study is the fact that we included a cohort of consecutive patients with a fixed regime of antithrombotic prophylaxis prior to and after the change in the local antithrombotic policy in July 2011. In our study all surgeons and cardiologists strictly adhered to both guidelines before and after July 2011. We think this adds to the external validation of our findings. Surprisingly, the number of bleeding events before and after policy change did not differ significantly. This might be due to the larger number of patients using acenocoumarol preoperatively, which is a predictor for bleeding, after policy change in 2011. However, when comparing the number of days on aspirin versus acenocoumarol bleeding events were significantly lower in the aspirin group. The number of thromboembolic events was similar in both analyses. Our study had the inherent limitations of being retrospective. Treatment was not randomly allocated. Second, medical files were mostly but not entirely complete. Ideally, future randomized clini-

cal trials comparing aspirin with VKA therapy are necessary to provide evidence-based recommendations for the implementation of optimal antithrombotic strategy.

In conclusion, our study shows a beneficial effect of aspirin compared to acenocoumarol one year after bioprosthetic aortic valve replacement, which reinforces the recommendation of aspirin by current guidelines.

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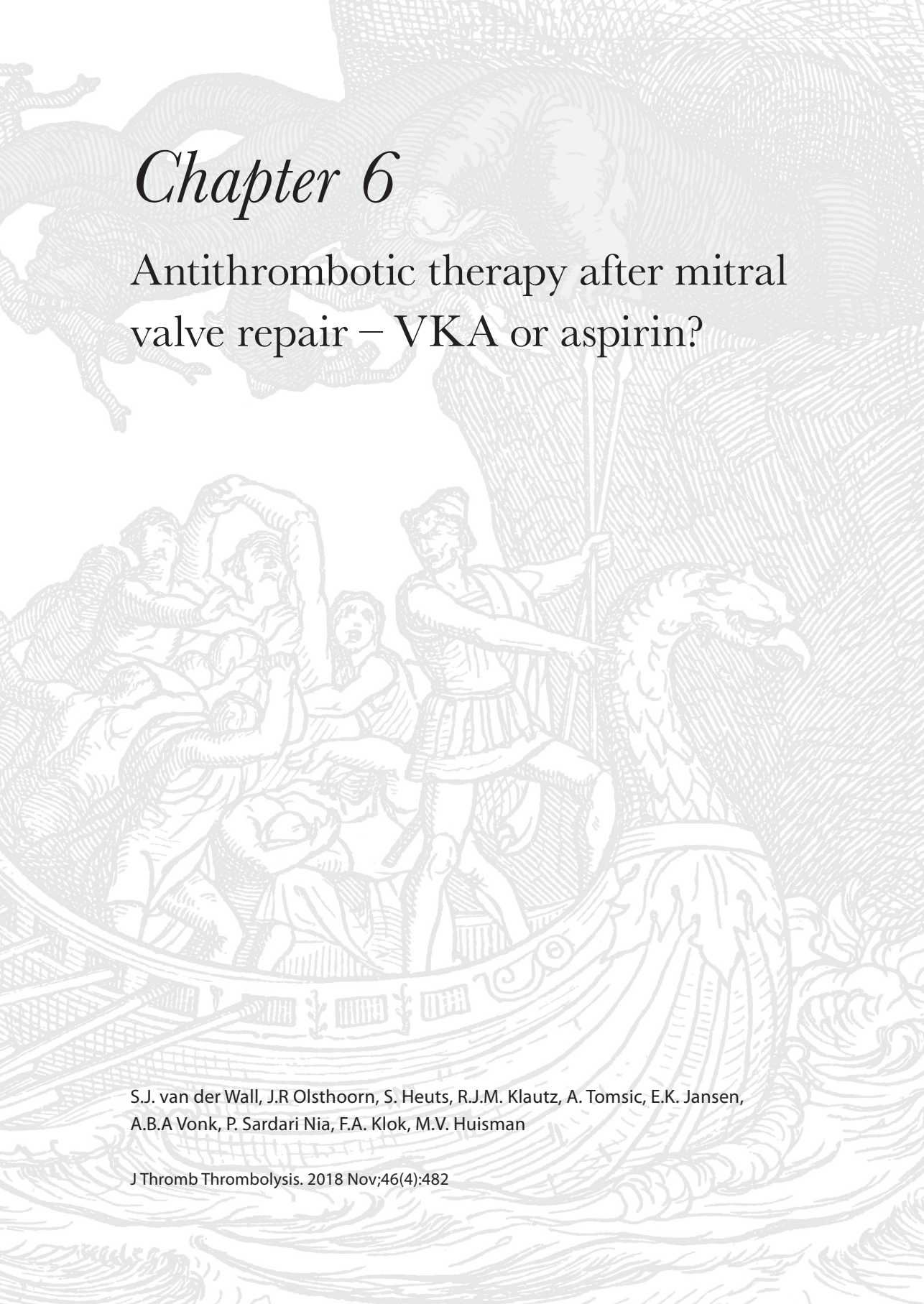
Chapter 6

Antithrombotic therapy after mitral valve repair – VKA or aspirin?



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ABSTRACT

Background

The optimal antithrombotic therapy following mitral valve repair (MVr) is still a matter of debate. Therefore, we evaluated the rate of thromboembolic and bleeding complications of two antithrombotic prevention strategies: vitamin K antagonists (VKA) versus aspirin.

Methods

Consecutive patients who underwent MVr between 2004 and 2016 at three Dutch hospitals were evaluated for thromboembolic and bleeding complications during three postoperative months. The primary endpoint was the combined incidence of thromboembolic and bleeding complications to determine the net clinical benefit of VKA strategy as compared with aspirin. Secondary objectives were to evaluate both thromboembolic and bleeding rates separately and to identify predictors for both complications.

Results

A total of 469 patients were analyzed, of whom 325 patients (69%) in the VKA group and 144 patients (31%) in the aspirin group. Three months postoperatively, the cumulative incidence of the combined end point of the study was 9.2% (95%CI 6.1-12) in the VKA group and 11% (95%CI 6.0-17) in the aspirin group (adjusted hazard ratio (HR): 1.6, 95%CI 0.83-3.1). Moreover, no significant differences were observed in thromboembolic rates (adjusted HR: 0.82, 95%CI 0.16-4.2) as well as in major bleeding rates (adjusted HR: 1.89, 95%CI 0.90-3.9).

Conclusions

VKA and aspirin therapy showed a similar event rate of 10% during three months after MVr in patients without prior history of AF. In both treatment groups thromboembolic event rate was low and major bleeding rates were comparable. Future prospective, randomized trials are warranted to corroborate our findings.

INTRODUCTION

Mitral valve repair (MVr) is recognized as the gold standard for degenerative mitral regurgitation. Compared to mitral valve replacement, repair results in improved survival, better preservation of postoperative left ventricular function and avoidance of the need for long-term anticoagulation treatment (1,2). The risk of thromboembolic events following MVr varies from 0.4% to 1.6 % per year, and reaches 2.5% during the first postoperative month, even with routine anticoagulation therapy (3,4). However, the appropriate antithrombotic therapy following MVr is still a subject of controversy. Recommendations from international guidelines for the postoperative antithrombotic management have been controversial (5-7), and are based on observational studies without conclusive results, or are provided without references supporting the recommendation (4,8-11).

Consequently, antithrombotic prophylaxis for the prevention of thrombotic events early after MVr varies widely among cardio-thoracic surgeons with a vitamin K antagonist (VKA) prescription varying from 46% to 64% in patients with sinus rhythm (12,13). The risk of thromboembolism secondary to a high incidence of new onset atrial fibrillation (AF) postoperatively and the thrombogenic tendency of the non-endothelialized repair components could motivate surgeons and cardiologists to prescribe VKA therapy for the first months after MVr (14). However, evidence is limited and more accurate knowledge of the postoperative antithrombotic treatment is required. Based on recent literature and anecdotal reports, we hypothesized that VKA treatment is associated with an increased risk of major bleeding events and no reduction in thromboembolic events (18).

We set out to perform a retrospective observational study to evaluate the rate of thromboembolic and bleeding and complications of two antithrombotic prevention strategies – one with VKA and one with aspirin – occurring within the first three postoperative months.

MATERIAL AND METHODS

Study design and patients

This study was a retrospective observational multicentre cohort study of consecutive adult patients who underwent MVr, to evaluate thromboembolic and bleeding complications of two antithrombotic strategies, VKA and aspirin. Data were collected from the databases of the departments of cardiothoracic surgery of the Leiden University Medical Centre (LUMC), VU University medical centre (VUmc) and Maastricht University Medical Centre (MUMC). Patients, who underwent a first MVr with or without concomitant tricuspid valve repair (TVr) between 2004-2016 in these three centres, were eligible. The post-operative care of these patients often took place in one of 16 affiliated regional

hospitals, in which all postoperative medical files were scrutinized for primary and secondary endpoints. Patients were excluded when they underwent other concomitant cardiac procedures than TVr, had previous cardiac surgery or were diagnosed with AF preoperatively. Other concomitant procedures were excluded because these lead to more heterogeneous patient groups. The institutional review board of the LUMC, VUmc and MUMC approved the study protocol and waived the need for informed consent due to the observational design.

Procedures and treatment

MVr was performed at the department of cardiothoracic surgery at the LUMC, VUmc or MUMC and involved implantation of an annuloplasty ring (Edwards Physio I or II mitral ring, Carpentier-Edwards Classic Annuloplasty Ring or Duran AnCore Ring for MVr, and Edwards MC3 tricuspid ring or Carpentier-Edwards Classic Annuloplasty Ring in case of concomitant TVr, *Edwards Lifesiences/Medtronic, USA*), and various concomitant techniques (leaflet resections, artificial chorda tendinae implant, chordal transposition, or edge-to-edge technique).

Group A comprised patients from the LUMC and VUmc hospitals, in which therapeutic doses of low-molecular-weight heparin (LMWH) nadroparin were given on the first postoperative day at 7600IU/day for patients < 50 kg, 11.400 IU/day for patients 50-70 kg, 15.200 IU/day for patients 70-100 kg and 19.000 IU/day for patients > 100 kg simultaneously with VKA. Treatment with nadroparin was continued until a VKA reached therapeutic levels, as shown by an international normalized ratio (INR) >2.0 on two consecutive days. VKA therapy was maintained for six to twelve weeks postoperatively and then discontinued at the discretion of the referring cardiologist and occasionally switched to aspirin. The target INR during VKA treatment was 2.0-3.0.

Group B consisted of patients from the MUMC hospital, in which prophylactic doses of nadroparin were started on the first postoperative day at 3750IU/day for patients <80kg, 5700 IU/day for patients 80-100 kg and 7600IU/day for patients > 100 kg simultaneously with aspirin 80mg once daily which was continued lifelong in patients with sinus rhythm. Nadroparin was stopped as soon as the patient was fully mobilized. In case of postoperative new onset AF that sustained for more than 24 hours, nadroparin and VKA were started analogous to the antithrombotic strategy used in the LUMC and VUmc.

Study Endpoints

The primary endpoint of this study was the combined incidence of thromboembolic and major bleeding complications three months following MVr. This double endpoint was the basis for determining the net clinical benefit of VKA as compared with aspirin. Since we anticipated a high incidence of postoperative new onset AF, we also compared

the primary endpoint in patients who did not develop AF during follow-up as well as in patients who received treatment according to the preferred strategy.

Secondary objectives were to evaluate the incidence rates of thromboembolic and major bleeding events separately and to identify predictors for bleeding and thrombotic complications. All thromboembolic and bleeding events were classified using the criteria for reporting mortality and morbidity after cardiac valve interventions respectively and those of the International Society on Thrombosis and Haemostasis respectively (15,16). Thromboembolic and bleeding complications occurring on the first postoperative day were not taken into consideration because both antithrombotic therapies were started this day. All suspected bleeding events were independently adjudicated by two expert physicians (F.K. and M.V.) who were blinded to treatment assignment. Disagreement was resolved by consensus.

Predefined candidate predictors for thromboembolic and bleeding events were defined according to the documentation provided by the treating physician, e.g. age, sex, prior arterial or venous thromboembolism, prior PCI, hypertension, history of smoking, preoperative use of anticoagulation therapy, left ventricular ejection fraction (LVEF), concomitant TVr, repeat thoracotomy and new onset AF. The cause of death was verified by reviewing the pathology report. In case autopsy had not been performed, the likely cause of death was verified with the treating physician. All patients were followed and censored at a maximum follow up period of three months, the date of last chart documentation, reoperation or outcome events, whichever came first.

Statistical analyses

Means (standard deviation (SD)) and medians (interquartile range (IQR)) to present baseline continuous baseline variables were used. For categorical variables, frequencies and percentages were used. Pearson's χ^2 test was used to compare the distribution of categorical variables, whereas the independent *t*-tests were used for normally distributed continuous variables. For analysis of primary and secondary objectives, cumulative incidences of bleeding and thromboembolic events of both antithrombotic strategies were estimated according to the Kaplan-Meier methods and presented with two-sided 95% confidence intervals (CI). A Cox proportional hazard model was used to compare both strategies, adjusted for age, gender, and baseline differences.

Backward conditional multivariate Cox-regressions analysis was used to evaluate possible predictors for thrombotic and bleeding events, using variables of clinical importance (age and gender) or that were identified to be relevant predictors ($P<0.1$) in univariate analysis. Data were analyzed using SPSS version 23 (SPSS, Chicago, IL, USA). A *P*-value below 0.05 was considered to be significant.

RESULTS

Patients

In the three participating cardiothoracic surgical centers, 809 patients underwent a first isolated MVr between 2004 and 2016. Of these patients, 340 (42%) were excluded for the following reasons: 109 did not receive treatment in one of the affiliated regional hospitals postoperatively (4.9%), 224 had preoperative AF (10%) and seven patients were lost to follow up (0.32%). The remaining 469 (21%) patients were included; 325 patients (69%) in group A and 144 patients (31%) in group B. The baseline characteristics of both groups are shown in **Table 1.** Their mean age was 61 (SD 12) and 280 patients (60%) were men. Patients in group A underwent concomitant TVr more frequently (22% vs. 4.9%). In group B, a LVEF below 40% and preoperative aspirin use were more present (9% vs. 3.8% and 27% vs. 18% respectively). A total of 220 patients (47%) developed new onset AF after surgery and 35 patients (7.5%) required a repeat thoracotomy.

Tabel 1. Baseline characteristics of 469 patients who underwent MVr.

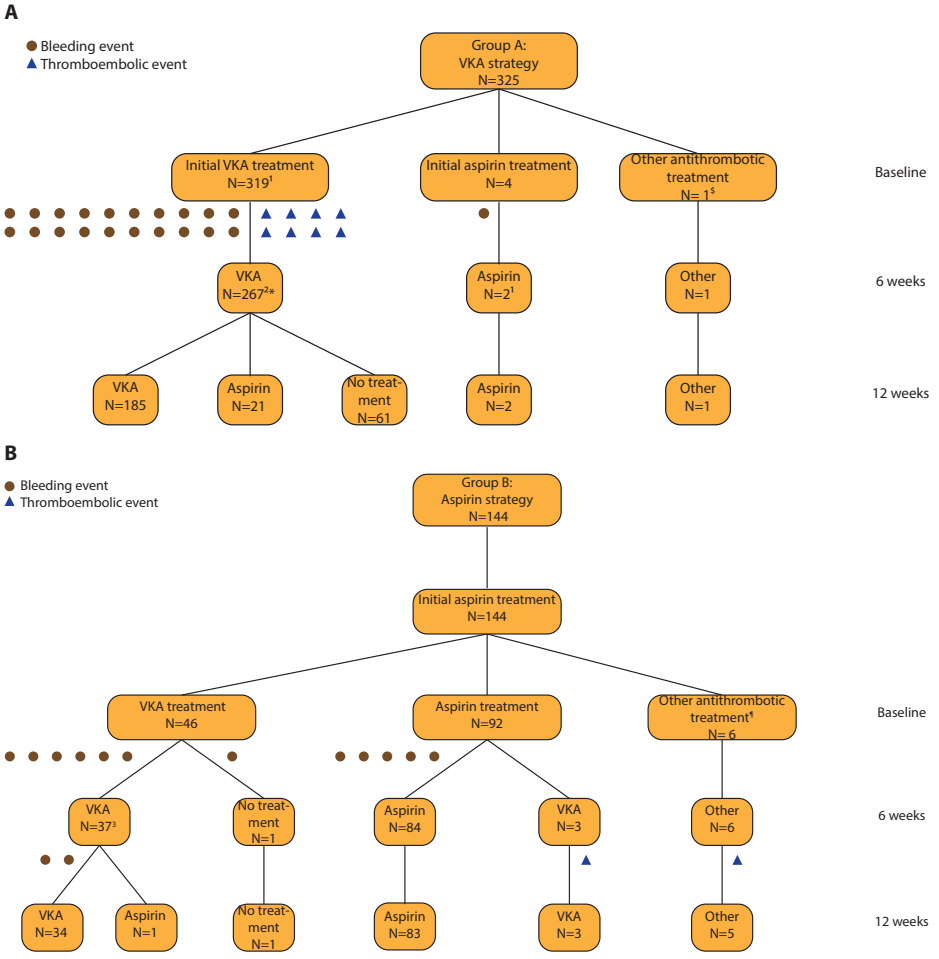
Patient characteristics		Group A: VKA (n=325)	Group B: Aspirin (n=144)
Age at operation, mean ± SD		60 ± 13	62 ± 11
Male, n (%)		195 (60)	85 (59)
Prior ischemic stroke, n (%)		7 (2.2)	8 (5.6)
Prior MI, n (%)		12 (3.7)	4 (2.8)
Prior PCI, n (%)		11 (3.4)	5 (3.5)
Prior VTE, n (%)		11 (3.5)	2 (2.6)
LV ejection fraction <40%, n (%)		12 (3.8)	13 (9)*
Diabetes, n (%)		17 (5.4)	5 (3.5)
Hypertension, n (%)		149 (47)	74 (51)
COPD, n (%)		29 (8.9)	15 (10)
History of smoking, n (%)		99 (31)	27 (19)
Preoperative anticoagulation use, n (%)			
	VKA	12 (3.7)	4 (2.8)
	Aspirin	57 (18)	39 (27)*
	Clopidogrel	3 (0.90)	2 (1.4)
	Dual AP	1 (0.30)	2 (1.4)
Active endocarditis at the moment of surgery, n (%)		24 (7.4)	9 (6.3)
Concomitant TVr, n (%)		72 (22)	7 (4.9)*

Note: SD = Standard Deviation, MI = Myocardial infarction, PCI = Percutaneous Coronary Intervention, VTE = Venous Thromboembolic Event, LV = Left Ventricular, VKA=Vitamin K Antagonist, AP=Antiplatelet, TVr = Tricuspid Valve Repair, *P-value below 0.05

Antithrombotic treatment

Of the 325 patients in group A, 319 patients (98%) were treated with VKA therapy, four (1.2%) with aspirin therapy and one patient (0.31%) with LMWH (**Figure 1A**). In group B, 92 of the 144 patients (64%) received aspirin, 46 patients (32%) VKA because of new onset AF and six patients (4.2%) received other antithrombotic therapy than VKA or aspirin (**Figure 1B**). Twenty-three patients (25%) in group B, who received initial aspirin therapy, experienced a single episode of new onset AF.

Figure 1. Flowchart of medication use and events of group A: VKA (A) group B: Aspirin (B).



Note: [1]1, [2]8, [3]1 patients censored for other reasons than study endpoints. *Data missing in 16 patients. [$]2 patients treated with direct oral anticoagulant (DOAC), 4 patients with clopidogrel, [¶] 1 patient treated with low-molecular-weight heparin.

VKA versus ASA

Table 2 shows the incidence of thromboembolic and bleeding events in each study group. The primary end point of the study – the composite of thromboembolic and bleeding events – was reached in 29/325 patients in group A (cumulative incidence: 9.2%, 95%CI 6.1-12) and in 16/144 patients in group B (cumulative incidence: 11%, 95%CI 6.0-17; adjusted hazard ratio (HR): 1.6, 95%CI 0.83-3.1). The composite of thromboembolic and bleeding events in patients without new onset AF occurred in 14/177 patients (cumulative incidence: 8.2%, 95%CI 4.1-12) in group A and 5/72 patients in group B (cumulative incidence: 8.1%, 95%CI 2.0-14.2; adjusted HR: 0.97, 95%CI 0.32-2.9). In patients who received initial treatment according to the preferable strategy, 28/319 patients experienced the primary endpoint in group A and 6/92 patients in group B during the first three months, for a cumulative incidence of 9.0% (95%CI 5.9-12) and 6.6% (95%CI 1.5-12) respectively (adjusted HR: 0.90, 95% CI: 0.35-2.3).

Table 2. Clinical outcomes within three months after MVr. [§]Numbers in parenthesis are cumulative incidence.

			Group A: VKA (N=325)	Group B: Aspirin (N=144)
Bleeding events				
	Major bleeding		21 (6.8)[§]	14 (9.1)
	Site			
		Chest	20	12
		GI tract	0	1
		Unknown	1	1
	Fatal bleeding		1	1
Thromboembolic events			8 (2.6)	2 (1.6)
	Type			
		Ischemic stroke	4	1
		TIA	4	0
		Left atrial thrombus	0	1
	Fatal ischemic stroke		0	1

Note: GI = Gastrointestinal, TIA = Transient Ischemic Attack, MI = Myocardial infarction, DVT = Deep Venous Thrombosis

Thromboembolism and bleeding

A total of 8/325 thromboembolic events occurred in group A after a median duration of 9 days (IQ 3.3-15) and 2/144 in group B after a median duration of 50 days (IQR 45-50), for a respective cumulative incidence of 2.6% (95%CI 0.84-4.4) and 1.6% (95%CI 0-3.8; adjusted HR: 0.82, 95%CI 0.16-4.2). 21/325 patients experienced a major bleeding in group A after a median duration of 12 days (IQR 8-15) and 14/144 patients in group B

after a median duration of 11 days (IQR 4.8-20), for cumulative incidences of 6.8% (95%CI 4.1-9.5) and 9.1% (95%CI 4.2-14) respectively (adjusted HR: 1.89, 95%CI 0.90-3.9). A total of 89% of the major bleeding events were pericardial tamponades, of which two were fatal (one in each group).

Other observations

During the study period, four patients died (cumulative incidence: 0.9%, 95%CI 0-1.9), of whom two died in group A and two in group B. Causes of death were pericardial tamponades (two patients), ischemic stroke and cardiac arrest.

Predictors for thromboembolism and major bleeding

Uni- and multivariate analysis of predictors for thromboembolic and major bleeding events in patients who received initial treatment according to antithrombotic strategy are shown in **Table 3.** Multivariate analysis revealed that only concomitant TVr was independently associated with an increased risk of bleeding events (odds ratio (OR): 2.8, 95%CI 1.4-5.7) for both groups. For thromboembolic events, no independent predictors were found by multivariate analysis.

Table 3. Predictors for major bleeding and thromboembolic events in 469 patients who underwent MVr.

	Major bleeding		**TE**	
Predictor	**Univariate RR (95%CI)**	**Multivariate RR (95%CI)**	**Univariate RR (95%CI)**	**Multivariate RR (95%CI)**
Age >60	0.94 (0.48-1.8)		0.71 (0.21-2.4)	
Female	1.2 (0.64-2.4)		0.37 (0.78-1.7)	
Prior ischemic stroke	-		3.1 (0.39-25)	
Prior MI	0.84 (0.12-6.1)		-	
Prior PCI	0.80 (0.11-5.8)		-	
Prior VTE	1.1 (0.15-8.0)		-	
LV ejection fraction < 40%	2.2 (0.78-6.3)		-	
Diabetes	1.9 (0.59-6.3)		-	
Hypertension	1.2 (0.62-2.3)		2.3 (0.61-9.1)	
History of smoking	0.78 (0.36-1.7)		1.5 (0.46-5.3)	
New onset AF	1.7 (0.88-3.4)		1.1 (0.33-4.0)	
Concomitant TVr	**2.8 (1.4-5.7)**	**2.8 (1.4-5.7)**	2.3 (0.59-8.9)	
Active endocarditis	1.7 (0.6-4.8)		1.5 (0.19-11)	

Note: MI = Myocardial infarction, PCI = Percutaneous Coronary Intervention, VTE = Venous Thromboembolic Event, LV = Left Ventricular, AF = Atrial Fibrillation, TVr = Tricuspid Valve Repair

DISCUSSION

VKA and aspirin therapy showed a similar event rate of 10% during the first three months after MVr in patients without prior history of AF. In both treatment groups thromboembolic event rate was low and major bleeding rates were comparable.

Nearly all bleedings occurred soon after surgery, particularly during the first two weeks after MVr. Interestingly, most of these were pericardial tamponades that required repeat thoracotomy. In contrast, the thromboembolic events occurred more dispersed throughout the first three months.

VKA versus aspirin treatment

We chose a primary combined endpoint of thromboembolic and bleeding rates because both events would have a comparable prognostic effect as both represent an important cause of death and disability after heart valve surgery (17). A comparison between VKA strategy (group A) and aspirin strategy (group B) revealed no difference in the combined outcome of thromboembolic and bleeding complications as well as for both outcomes separately occurring within three months after MVr. As expected, a third of the patients in group B could not follow the aspirin strategy because of new onset AF and received VKA treatment instead of aspirin therapy. Both of these group B treatment groups experienced major bleeding events to a similar extent. However, after exclusion of AF patients in the entire study population as well as analysing patients who received treatment according to the preferable strategy, again no difference in the combined endpoint was found, despite a group B population with solely aspirin use. Of note, three thromboembolic events in the VKA group occurred within the first four days during which VKA treatment still had not yet reached therapeutic levels. The observed three-month cumulative incidence for thromboembolic events is in aligned with those reported by previous studies (18,4). The observed incidence of major bleeding events was slightly higher than described in previous reports, probably due to the adjudication process of postoperative pericardial tamponade (19,20). Pericardial effusion alongside signs of hemodynamic instability was adjudicated as a pericardial bleeding, whereas these events might not be considered as (major) bleedings in previous studies.

Perspective of international guidelines

Recommendations from international guidelines are contradictory to our results, favouring either VKA or aspirin as postoperative thromboprophylaxis three months after MVr (6,21,5). Three former retrospective studies have compared antiplatelet with anticoagulation therapy in patients after MVr (8,22,20,19). Two studies found no differences in stroke and bleeding rate of early VKA treatment compared with aspirin therapy, suggesting that VKA treatment might not be necessary (22,20). The largest study to date

by Paparella et al (19) found less bleeding and comparable arterial thromboembolic events in patients treated with aspirin six months following MVr. However, in contrast to our study, no data on AF were reported and assigned treatment was mainly chosen by the surgeons' preference. A small study by Aramendi et al (8) found a beneficial effect of antiplatelet therapy in preventing thromboembolic events compared with VKA treatment with no increased risk of bleeding. Thus, these four studies suggest aspirin use after MVr. This contradicts the recommendation of VKA use over aspirin by the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology/European Association of Cardiothoracic Surgery (ESC/EACTS) guidelines (6,21). The ACC/AHA recommendations are based on one observational cohort study which found a high 30-day ischemic stroke incidence of 1.5%, despite VKA treatment (21,4). The ESC recommendation is provided without references, illustrating the paucity of information (6). Since recommendations from guidelines are based on retrospective and underpowered studies, the optimal thromboprophylaxis after MVr remains controversial and a frequent matter of debate. However, based on the scarcity of data, our results might suggest a reassessment of the recommendations from international guidelines.

Predictors

In our study, only concomitant TVr was found to be an independent predictor for major bleeding events. Concomitant TVr might have been a more difficult procedure with prolonged cardiopulmonary bypass duration, leading to dysfunction of platelets, which is associated with major cause of excessive bleeding in the early postoperative period (23,24). Other not predefined predictors, such as surgery duration, preoperative hematologic laboratory values and surgical techniques might also have contributed to the occurrence of early bleeding events. Consistently with earlier findings, no independent predictors were found for thromboembolic events (18).

Clinical perspective

When considering the appropriate antithrombotic treatment after MVr, the thrombotic risk secondary to the endothelialization process and new onset AF could be a good rationale for physicians to prescribe VKA treatment. During the first three postoperative months, the exposure of circulating blood to non-endothelialized repair components can cause thrombus formation and even endocarditis, particularly due to a relatively slower blood flow in the left atrium compared to other parts of the heart. AF is a common postoperative cardiac arrhythmia after MVr occurring in approximately 24-35% of the patients, even after two postoperative weeks (25,14). In this study we found this incidence of new onset AF to be 47%. VKA treatment, however, has many disadvantages, including need for frequent laboratory monitoring, variability of dose response and

drug and food interactions while in contrast aspirin does not require monitoring and dosage adjustments. Consequently, for practical reasons, aspirin might be preferable as antithrombotic treatment compared to VKA in patients with sinus rhythm. Therefore, the choice of antithrombotic treatment in patients without prior history of AF should be individualized based on patient-specific considerations, such as risk factors for AF, compliance with treatment and frailty. Despite the lack of prospective studies specifically evaluating treatment with direct oral anticoagulants (DOACs) in patients with mitral valve repair, subanalysis of DOAC AF trails have showed a similar overall efficacy and safety as compared with VKA in patients with valvular heart disease, including mitral valve repair (26). However, international guidelines do not recommend the use of DOACs during the first three to six postoperative months in patients with AF (5-7).Future prospective randomized trials are warranted to provide conclusive results about DOAC treatment in the early postoperative phase after mitral valve repair in patients with and without AF.

Strengths and limitations

The strength of this study is the large cohort of consecutive patients providing novel and clinically relevant data on the antithrombotic strategy after MVr. Moreover, the study population was rather homogeneous due to the exclusion of concomitant procedures that might lead to different patient groups (i.e. AF, other valve and coronary atherosclerotic surgery).

Our study had several limitations as well. First, a direct comparison between patients treated with VKA and aspirin would have been preferable but the high incidence of AF makes such a trial difficult to perform. A large number of patients would be required, in particular patients receiving aspirin. Second, antithrombotic treatment was not randomly allocated due to the retrospective study design. Third, no data was available on individual INR measurements and thus the time during which VKA treated patients were in therapeutic range is unclear. Fourth, we performed a multi-centre study with inherent perioperative variabilities. Ideally, future prospective, randomized clinical trials are warranted to provide evidence-based recommendations for the implementation of appropriate antithrombotic strategy after MVr.

In conclusion, VKA and aspirin therapy showed a similar event rate of 10% during three months after MVr in patients without prior history of AF. In both treatment groups thromboembolic event rate was low and major bleeding rates were comparable. Future prospective, randomized trials are warranted to corroborate our findings.

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Part 3

Idarucizumab as antidote of dabigatran

Chapter 7

Performance of idarucizumab as antidote of dabigatran in daily clinical practice

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ABSTRACT

Aims

Because practice-based data on the usage of idarucizumab for urgent dabigatran reversal are unavailable we evaluated the appropriateness of idarucizumab usage, its hemostatic effectiveness and clinical outcomes.

Methods

An observational cohort study was performed including consecutive patients who were treated with idarucizumab between 2016 and 2018. Appropriate usage was assessed with predefined criteria. Post-reversal effectiveness was evaluated according to ISTH recommendations. Patients were followed for 90 days for occurrence of thromboembolism, (re-)bleeding and death.

Results

Idarucizumab was used in 88 patients, of whom 53 (60%) presented with severe bleeding (20 gastrointestinal and 18 intracranial) and 35 (40%) requiring urgent surgical intervention. Use of idarucizumab was judged inappropriate in 25 patients (28%). Effective hemostasis was achieved in 32 of 48 (67%) bleeding patients in whom assessment was possible. Seven of 16 patients with major bleeding who did not achieve effective hemostasis (five intracranial) died, compared to two of 32 patients with effective hemostasis (relative risk: 7.0, 95% confidence interval 1.6-30). Four patients (4.2%) developed thromboembolism (2 (2.1%) within 30 days) and four patients (4.2%) re-bleeding, all within 10 days. Seventeen patients (19%) died; 10 (11%) within five days.

Conclusion

In this practice-based cohort, idarucizumab use was considered inappropriate in 28% of patients. Effective hemostasis was achieved in two third of bleeding patients and was associated with lower mortality risk. Clinical outcomes were similar to those observed in the RE-VERSE AD trial, comprising re-bleeds and thromboembolism, and a high mortality rate.

INTRODUCTION

Because of its favourable benefit-risk profile compared to vitamin K antagonists (VKA), dabigatran etexilate (Pradaxa®) is widely used for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation and for the prevention and treatment of venous thromboembolism (1, 2). However, as for all anticoagulants, bleeding, including life-threatening or fatal bleeding, remains a relevant side effect. The lack of a reversal agent has been perceived as a concern to both patients and clinicians which until recently has been an obstacle for direct oral anticoagulant (DOAC) use in many patients.

The specific reversal agent Idarucizumab (Praxbind®), a monoclonal antibody fragment that binds dabigatran with high affinity, has been approved by the U.S. Food and Drug Administration and the European Medicines Agency for urgent dabigatran reversal (3-5). This approval was based on the results of the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial which showed rapid and complete reversal of dabigatran activity in patients with uncontrolled or life-threatening bleeding or undergoing an emergency procedure (6). Further insight on the clinical use of idarucizumab is only available from case reports and one small retrospective study demonstrating safe and effective idarucizumab administration in 31 patients with intracranial bleeding or ischemic stroke prior to thrombolysis (7, 8). Even so, current international guidelines recommend idarucizumab usage for urgent dabigatran reversal in the presence of life-threatening bleeding or urgent surgery associated with high risk of bleeding (9, 10). It remains nonetheless to the clinician's discretion to decide in which clinical setting usage of idarucizumab is appropriate.

Since data on idarucizumab in daily practice are scarce, we set out to perform an observational study aiming to determine the appropriateness of idarucizumab usage as well as the hemostatic effectiveness and clinical outcomes in daily practice.

METHODS

Study design and population

This was an observational, multicentre cohort study including consecutive patients who were treated with idarucizumab between 2016 and 2018, with the aim of evaluating appropriate usage, hemostatic effectiveness and 90-day clinical outcomes. A representative from manufacturer Boehringer Ingelheim provided a list of 20 major idarucizumab distributing Dutch hospital pharmacies which were all approached for participation. Five of them replied not to have dispensed idarucizumab, three did not comply with the request and 12 provided all available information. Subsequently, data were collected by scrutinizing medical records, including medical notes, laboratory results, radiology

reports and other relevant details. No exclusion criteria were applied. The institutional review board of the LUMC centrally approved the study and waived the need for informed consent because of its observational non-interventional design.

Study outcomes

The primary objective was to assess the appropriateness of idarucizumab usage. Each individual administration was adjudicated independently by two expert physicians (F.K. and M.V.) using criteria listed in **Table 1.** These criteria were predefined and based on an expert consensus of the International Society on Thrombosis and Haemostasis (ISTH) for reversal of direct oral anticoagulants (DOACs) (11). These guidance indications include life-threatening/uncontrollable bleeding, bleeding into a critical organ or closed space, prolonged bleeding despite local hemostatic measures, high risk of recurrent bleeding because of overdose or delayed clearance of dabigatran, and need for an urgent intervention associated with a high risk of bleeding.

In line with the RE-VERSE AD trial (6), bleeding was considered uncontrollable if one or more of the following criteria were met: symptomatic intracranial bleeding, a reduction in hemoglobin (Hb) of at least 5 g/dL, transfusion of at least 4 units of blood or packed cells, bleeding requiring use of intravenous inotropic agents or necessitating surgical intervention. An urgent intervention was defined as one that could not be delayed for at least 8 hours. We added indicators for the presence of dabigatran plasma levels as a criterion for appropriateness. These indicators comprised a sensitive activated Partial Thromboplastin Time (aPTT), diluted Thrombin Time (dTT) or ecarin clotting time (ECT) laboratory test result above the upper limit of normal (according to fixed cut-off points of individual hospitals) and/or a self-reported time of last dabigatran intake. Discrepancies were resolved independently by a third party, consisting of a relevant specialized expert physician who was selected ad hoc.

Secondary objectives were 1) to assess hemostatic efficacy after administration for urgent reversal in bleeding events, and 2) to evaluate the incidence of 90-day clinical outcomes, comprising thromboembolism, (re-)bleeding and death. Hemostatic efficacy was assessed in accordance with standardized definitions published by the ISTH (12). Additional chart data were collected for bleeding course, need for blood products, additional procedures, and , for intracranial bleeding solely, results from repeat computed tomography scans and change in neurological status. Thromboembolic events comprised objectively verified arterial (i.e. stroke, transient ischemic attack, myocardial infarction or arterial thromboembolism) or venous thromboembolisms (i.e. deep vein thrombosis and pulmonary embolism). Bleeding complications were classified using the ISTH criteria for major bleeding (13). The cause of death was verified by reviewing the pathology report. In case autopsy had not been performed, the likely cause of death was verified with the treating physician.

Table 1. Proposed criteria for proper idarucizumab usage. *If test result is available prior to administration

Reason for idarucizumab usage	Adjudication category	
	Appropriate usage	**Inappropriate usage**
Intervention	Proper indication ISTH guidance Need for urgent intervention that cannot be delayed for drug clearance (within eight hours) Emergency intervention in patients at high risk for procedural bleeding Indicators for presence of circulating dabigatran Dabigatran intake <72h Prolonged aPTT, ECT or dTT*	Improper indication ISTH guidance Intervention that can be delayed to permit dabigatran clearance Elective surgery Absence of indicators for circulation dabigatran
Bleeding	Proper Indication ISTH guidance Uncontrollable hemorrhage Closed space or critical organ (intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, intramuscular with compartment syndrome Persistent major bleeding or risk of recurrent bleeding because of delayed dabigatran clearance Indicators for presence of circulation dabigatran Dabigatran intake <72h Prolonged aPTT, ECT or dTT*	Improper indication ISTH guidance Major (GI) bleeds that respond to supportive measures Absence of indicators for circulating dabigatran

Note: ISTH=International Society on Thrombosis and Haemostasis, aPTT=activated Partial Thromboplastin Time, dTT=diluted Thrombin Time, ECT=ecarin clotting time, GI=Gastrointestinal.

Statistical analysis

Means (standard deviation (SD)) and medians (interquartile range (IQR)) were used to present continuous variables and analyzed with t-test for normal and the Mann-Whitney test for skewed distributions. The categorical variables were described by proportions (n) and percentages (%), and compared using relative risks (RRs) with associated 95% confidence intervals (CI). Data were analyzed using SPSS version 23 (SPSS, Chicago, IL, USA). A *P*-value below 0.05 was considered to be significant.

RESULTS

Study population

Demographic and clinical characteristics of all consecutive 88 patients who were treated with idarucizumab for urgent dabigatran reversal are listed in **Table 2**. Among the 12 hospitals, the number of administrations varied from one to 14 during the two year

study period. Fifty-three (60%) patients presented with bleeding and 35 (40%) patients required urgent intervention. The mean age was 76 (SD ± 9) years and 51 patients (58%) were males. Nearly all patients (96%) had atrial fibrillation (AF) as primary indication for dabigatran use. The last self-reported dabigatran intake was > 24 hours in 11 patients (13%). Administration of idarucizumab occurred at the hospital ward (49%), the emergency room (34%), operating theatre (9.1%) or intensive care unit (6.8%). The aPTT was measured in 38 patients (43%) and was prolonged in 32/38 patients (84%). Specific dabigatran tests (ECT or dTT) were available in 10 of 12 included hospitals (83%) but were used in only 16 patients (18%). Of the 53 patients who presented with bleeding,

Table 2. Baseline characteristics of 88 patients who received idarucizumab. Patient used *75mg dabigatran BID and †rivaroxaban.

Characteristic		**Intervention (n=35)**	**Bleeding (n=53)**	**Total (n=88)**
Age, mean ± SD		74 ± 9	78 ± 9	76 ± 9
Male, no. (%)		19 (54)	32 (60)	51 (58)
eGFR (ml/ms), no. (%)	>90	5 (14)	5 (9.4)	10 (11)
	61-90	16 (46)	23 (43)	39 (44)
	30-60	7 (20)	20 (38)	27 (31)
	<30	5 (14)	3 (5.7)	8 (9.1)
	Missing	2 (5.7)	2 (3.8)	4 (4.5)
Dabigatran dosage BID, no. (%)	150mg	18 (52)	18 (34)	36 (41)
	110mg	16 (46)	34 (64)	50 (57)
	Other	1 (2.9)*	1 (1.9) †	2 (2.3)
Dabigatran indication, no. (%)	AF	32 (91)	52 (98)	84 (96)
	VTE	2 (5.7)	1 (1.9)	3 (3.4)
	Unknown	1 (2.9)	0	1 (1.1)
Last intake of dabigatran until administration (h), no. (%)	<24	32 (91)	44 (83)	76 (86)
	24-47	3 (8.6)	4 (7.5)	7 (8.0)
	48-71	0	2 (3.8)	2 (2.3)
	>72	0	2 (3.8)	2 (2.3)
	Missing	0	1 (1.9)	1 (1.1)
Laboratory tests prior to idarucizumab administration				
aPTT (s)	No (%)	8 (22)	30 (57)	38 (43)
	Above normal range, no (%)	8 (100)	24 (80)	32 (84)
Dabigatran (ECT/ dTT) (s)	No (%)	8 (23)	8 (15)	16 (18)
	> 30 ng ml^{-1}	7 (88)	8 (100)	15 (94)
	> 50 ng ml^{-1}	5 (63)	7 (88)	12 (75)

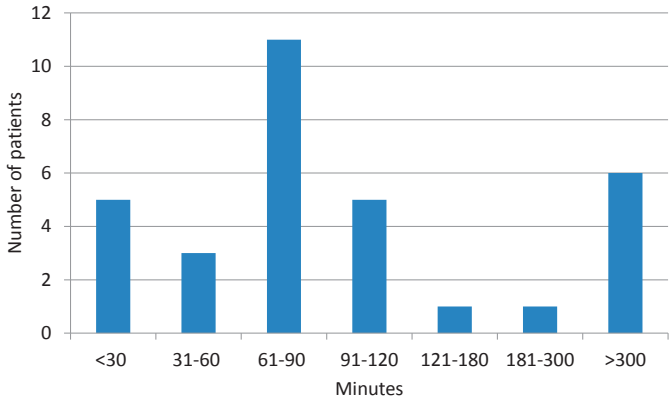
Note: eGFR=estimated Glomerular Filtration Rate, BID=Twice a day, AF=Atrial Fibrillation, VTE=Venous Thromboembolism, aPTT=activated Partial Thromboplastin Time, TT= Thrombin Time, dTT=diluted Thrombin Time, ECT=ecarin clotting time, NSAID=Non-Steroidal Anti-inflammatory Drugs, SSRI=Selective Serotonin Reuptake Inhibitors

most had gastrointestinal (38%) or intracranial bleeding (34%; **Table 3**). Of the 35 urgent interventions, most were performed in the abdominal region (39%). The time between administration of idarucizumab and initiation of intervention varied greatly (**Figure 1**). Each patient received the recommended dosage of idarucizumab (single administration of two times 2.5 grams).

Table 3. Bleeding events and interventions of 88 patients who received idarucizumab. All data is presented as n (%).

Intervention (n=35)		**Bleeding (n=53)**	
Abdominal	14 (40)	Gastrointestinal	20 (38)
Cardiovascular	8 (23)	Intracranial	18 (34)
Fractures	5 (14)	Pericardial	7 (13)
Nervous system	3 (8.6)	Lung	2 (3.8)
Skin	2 (5.7)	Other	6 (11)
Lung	1 (2.9)		
Eye	1 (2.9)		
Pancreatic/hepatobiliary	1 (2.9)	Traumatic	9 (17)

Figure 1. Time between first idarucizumab infusion and initiation of procedure in 31 patients in whom this duration could be determined.



Appropriateness of idarucizumab usage

Inappropriate usage of idarucizumab occurred in 25 patients (28%): 14 of 35 patients (40%) requiring intervention and 11 of 53 patients (21%) presenting with bleeding (**Supplemental table S1**). All 14 interventions could have been delayed for at least eight hours and eight of these 11 (72%) bleeding complications were not considered uncontrollable. Three bleeding patients (5.7%) had no dabigatran plasma levels; two had a last intake >72 hours as well as normalized aPTT levels, and one patient used

rivaroxaban instead of dabigatran. Nearly all bleeding events in which the administration was considered inappropriate were located in the gastrointestinal tract (73%).

Hemostatic effectiveness

Treatment with idarucizumab was considered effective in 32 of 48 (67%) bleeding patients in whom assessment was possible (**Table 4**). No significant difference was observed between the effectiveness of intracranial and extracranial bleeding (RR: 1.2, 95%CI 0.53-2.7) as well as traumatic and non-traumatic bleeding (RR: 1.5, 95%CI 0.40-6.1). Seven of 16 patients (44%) with bleeding (five intracranial) who did not achieve effective hemostasis died compared to two of 31 patients (6.5%) with effective hemostasis (RR: 7.0, 95%CI 1.6-30). Effective hemostasis of appropriate idarucizumab usage was comparable to all administrations, achieved in 28 of 38 patients (74%).

Table 4. Effectiveness of hemostasis in 53 patients with bleeding events. *Other bleedings were: lung, retroperitoneal, skin or fractures.

		Effective	Ineffective	Unclear
Bleeding type, n (%)	GI bleeding	15 (75)	5 (25)	0
	ICH	10 (56)	6 (33)	2 (11)
	Pericardial	4 (57)	1 (14)	2 (29)
	Other*	3 (38)	4 (50)	1 (13)
	Traumatic	3 (33)	4 (44)	2 (22)
	Non-traumatic	12 (29)	27 (64)	3 (7.1)
Mortality, n (%)		2 (6.3)	7 (44)	3 (60)
Additional procedures, n (%)		9 (75)	2 (17)	1 (8.3)
Days of hospital stay, mean (IQR)		9 (4-13)	10 (3-11)	6 (3-11)
Total, n (%)		32 (60)	16 (30)	5 (9.4)

Note: GI=Gastrointestinal, ICH=Intracranial Hemorrhage, IQR=Inter-Quartile Range

CLINICAL OUTCOMES

Thromboembolic and bleeding complications

Four thrombotic and four (re-)bleeding complications occurred during the 90-day follow up, all in patients who initially had presented with bleeding (**Table 5**). Thrombotic events comprised two ischemic strokes, occurring on day one (before anticoagulation resumption) and 41 (after anticoagulation resumption), and two pulmonary embolisms (one fatal), occurring on day five (before anticoagulation resumption) and 21 (after dabigatran resumption). A 65-year old male who developed ischemic stroke at the first day after idarucizumab administration also developed a major pericardial re-bleeding after six days after restart of anticoagulation therapy. Other re-bleeding events comprised

of a fatal pericardial (after dabigatran resumption) and two minor bleedings (before anticoagulation resumption), all occurring within 10 days and at the same anatomical location of the index presentation.

Table 5. Characteristics of patients with 90-day adverse outcome. *Therapeutic dosage.

Event	Time from idarucizumab (days)	Time until restart of anticoagulation (days)		Age (y)	Dabigatran dose BID (mg)	Type of index bleeding
		Parenteral*	Dabigatran			
Thromboembolism						
Ischemic stroke	1	2	Unknown	65	150	Pericardial
Fatal pulmonary embolism	5	-	-	92	110	ICH
Ischemic stroke	21	-	4	73	150	ICH
Pulmonary embolism	41	-	1	79	110	GI
Re-bleeding						
GI (minor)	3	-	-	73	150	GI
Lung (minor)	6	-	6	85	110	Lung
Pericardial (major)	6	2	-	65	150	Pericardial
Fatal pericardial (major)	9	-	-	82	110	Pericardial

Note: ICH=Intracranial Hemorrhage, GI=Gastrointestinal

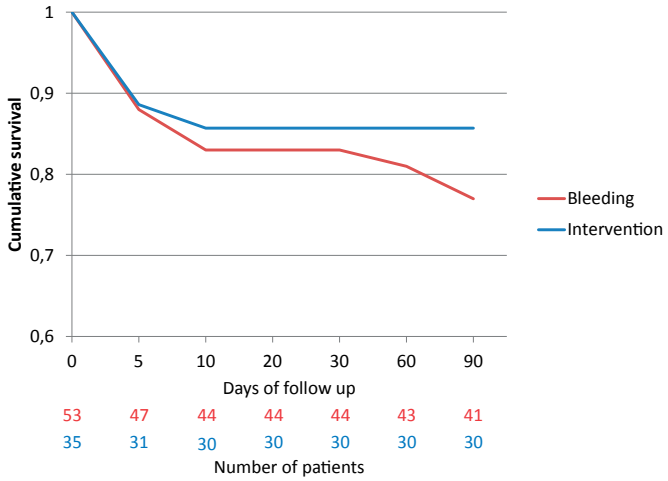
Deaths

During the 90-day follow up, 17 patients died (19%); 10 (11%) within five days. Of these 17 patients, 12 had presented with bleeding (six intracranial) and five underwent urgent intervention. The Kaplan-Meier curve of cumulative survival is shown in **Figure 2**. Causes of death within five days were: sepsis (three patients), postoperative shock (three patients; one possibly related to bleeding), intracranial bleeding (two patients), pericardial bleeding (one patient) and lung bleeding (one patient). Other causes of death after five days were sepsis (three patients), unknown (two patients), intracranial bleeding (one patient), pericardial bleeding (one patient) and pulmonary embolism (one patient).

Antithrombotic therapy resumption

Overall, antithrombotic therapy was restarted in 60 of 88 patients (68%); in 31 of 35 patients (89%) requiring intervention after a median of 3 days (IQR 1-5) and in 30 of 53 patients (57%) presenting with bleeding after a median of 6 days (IQR 3-11). A total of 51 patients (58%) restarted dabigatran and nine patients were switched to other antithrombotic regimens; five to VKA, three to LMWH (one prophylactic and two therapeutic) and one to apixaban.

Figure 2. Kaplan Meier 90-day survival curve of 88 patients after idarucizumab administration, stratified by reason for usage.



DISCUSSION

The main findings of this practice based cohort study were that idarucizumab usage was considered inappropriate in 28% of patients, mostly due to interventions that could have been delayed and gastrointestinal bleeding complications that might also have responded to supportive measures alone. For patients presenting with bleeding, two third achieved effective hemostasis after idarucizumab administration, which was associated with lower mortality risk. In line with the REVERSE-AD study, we observed a 4.2% rate of thromboembolic and bleeding events, and a mortality rate of 19% within 90 days (6).

The predefined criteria for appropriateness were based on the recent ISTH guidance for DOAC reversal which is in line with international guideline recommendations of the European Society of Cardiology (2016) and the American Heart Association (2017) (9-11). After adjudication, forty percent of interventions could have been delayed for at least eight hours and 15% of bleedings were located in the gastrointestinal tract that might also have responded to supportive measures alone. Inappropriate usage is likely the result of the acute critical care setting in which a prompt decision is required, as is illustrated by one patient who incorrectly received idarucizumab while using rivaroxaban. In addition, hospital logistics might also have played an important role in the decision not to delay interventions, as operating room schedules may not always allow awaiting full dabigatran clearance. Moreover, it might have been difficult to foresee the time needed to await dabigatran clearance in patients with moderate to severe renal impairment. In order to prevent inappropriate idarucizumab usage, clinicians should attentively manage dabigatran intake and assess the urgency of the intervention as well

as the bleeding severity when deciding upon administration. Ideally, the decision to administer idarucizumab should be made by a multidisciplinary team.

Results of laboratory test may guide the decision whether or not to administer idarucizumab, except for patients with life-threatening conditions in whom a rapid decision is required. Specific dabigatran tests for accurate estimation of dabigatran plasma concentrations, i.e. the diluted thrombin time (dTT) and the ecarin clotting time (ECT), were infrequently used in our study, although these tests were available in 10 of 12 included hospitals. Applying these tests however requires careful preparation of the specific reagents and materials as well as the presence of an experienced laboratory worker to perform the procedure and analyses. This probably resulted in the low rate of use in the acute setting. The fact that the aPTT test was frequently used to estimate dabigatran plasma levels supports this conclusion.

Inappropriate usage has some important drawbacks. Despite an observed non-procoagulant activity of idarucizumab (5), the attributable thrombotic risk has not yet accurately been determined. Inappropriate usage also significantly increases health care costs as the average wholesale price package of two idarucizumab 2.5 g/50 mL vials is approximately €2600. In addition, there is still insufficient knowledge about the risk of hypersensitivity and significant drug interactions associated with idarucizumab (14). Hereditary fructose intolerance could, for instance, induce a serious adverse reaction due to sorbitol excipients that are processed in the idarucizumab compound (3). Thus, inappropriate usage has impact on both patients' safety as well as healthcare cost.

Our observation of effective hemostasis is similar to those reported in the Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors (ANNEXA-4) study and to Sarode *et al.* (2013) evaluating the use of prothrombin complex concentrates (PCC) in VKA (15, 16). This similar effectiveness indicates that these reversal agents are all effective or, alternatively, have minimal or no effect. In the present study, bleeding localization was not related to effectiveness. However, as may be expected, failure to achieve effective hemostasis was associated with higher mortality risk. These comprised mostly patients with intracranial bleeding who are generally at high risk of poor outcomes (17).

The 90-day thromboembolic (4.2%), bleeding (4.2%) and mortality (19%) rates were consistent with those reported by the large RE-VERSE AD trial (6). This clearly reflects the similarities between study populations, involving comparable baseline characteristics and a similar distribution of bleedings and interventions. The observed 5-day mortality rate of 11% underlines the poor prognosis of the patients enrolled with uncontrollable bleeding or requiring emergency interventions. Moreover, the most frequent cause of death does not seem related to bleeding or thromboembolism, but may be driven by the underlying disease. Importantly, it is difficult to analyze the real impact of idarucizumab on patient outcome as there can be no control group for ethical reasons. The 2.1% 30-day thromboembolic rate in our study was lower than those reported in previous

studies evaluating prothrombin complex concentrate (PCC) for the reversal of VKA or Xa-inhibitors, in which thrombotic rates between 4% and 8% were demonstrated (15, 18, 19). Although an indirect comparison, this difference might be explained by the fact that we observed a large part of patients requiring interventions, in which anticoagulation therapy was more rapidly and frequently resumed, whereas these studies only included patients with bleeding (15, 18, 19). The timing of resumption after a bleeding episode is clearly more difficult. A recent ESC consensus recommends resumption after major bleeding as soon as the thrombotic risks outweigh the re-bleeding risks, in most cases within one week (20). Although this was consistent with an observed median duration of six days in our study, all thrombotic and (re-) bleeding events occurred in patients presenting with bleeding. Results of randomized trials evaluating optimal anticoagulation resumption after severe bleeding are eagerly awaited.

To our knowledge, this is the largest practice-based cohort of consecutive patients treated with idarucizumab. No exclusion criteria were applied, which makes the study generalizable to the population treated with idarucizumab. Also, standardized ISTH criteria were used for the evaluation of appropriate usage (11). Each case was independently adjudicated. Our data provide further insight into clinical practice in different situations in which idarucizumab currently is used and its role for the management of urgent dabigatran reversal.

The most important limitation of our study was the retrospective design. Inherently, we might not have accurately reconstructed the line of clinical reasoning in the acute setting. To deal with this issue, medical reports were meticulously scrutinized before the independent adjudication process occurred. In addition, the hemostatic effectiveness could not be determined in 10% of patients because required ISTH criteria for this assessment could not completely be retrieved from the medical reports.

In conclusion, idarucizumab usage was considered inappropriate in 28% of patients, mostly due to interventions that could have been delayed and gastrointestinal bleeding complications that might have responded to supportive measures alone. Of note, the criteria applied to judge appropriateness have not been tested in clinical trials and may not fully reflect daily clinical care on crowded emergency rooms. Two third of bleeding patients achieved effective hemostasis which was associated with a lower mortality risk compared to patients with ineffective hemostasis. Clinical outcome of patients treated with idarucizumab was similar to those observed in the RE-VERSE AD trial(6), comprising (fatal) re-bleeds and thromboembolism, and a high mortality rate.

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Chapter 8

Idarucizumab for dabigatran reversal in the management of patients with gastrointestinal bleeding

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ABSTRACT

Background

Although dabigatran has a favourable risk-benefit profile compared to vitamin K antagonist therapy for venous thromboembolism and non-valvular atrial fibrillation, major bleeding events - including gastrointestinal (GI) bleeding - may occur. Therefore, our aim was to provide insights on the efficacy and safety of idarucizumab for urgent dabigatran reversal in patients with major GI bleeding.

Methods

Patients with uncontrollable GI bleeding were enrolled from June 2014 through July 2016 in RE-VERSE AD™, a prospective, multi-centre, open-label study of idarucizumab and were followed for 90 days for primary and secondary outcomes. Patients were to receive a 5g dose of intravenous idarucizumab, administered as two bolus infusions of 2.5g no more than 15 minutes apart.

The primary endpoint was the maximum reversal of dabigatran anticoagulation within four hours after administration of idarucizumab as measured by the dabigatran-specific assays diluted thrombin time (dTT) and ecarin clotting time (ECT). Further endpoints included investigator-reported bleeding cessation within the first 24 hours, and incidence of re-bleeding, thromboembolic events and/or mortality.

Result

GI bleeding occurred in 137 patients enrolled in REVERSE-AD, of which 48 (35.0%) were upper GI tract in origin, 43 (31.4%) were lower, and 46 (33.6%) were either both or unknown. Complete reversal of dabigatran was observed in 118 of 121 (97.5%) patients with an elevated dTT at presentation and 95 of 131 (72.5%) with an elevated ECT, and was similar for upper and lower GI bleeding. Bleeding cessation within 24 hours was reported in 92 of 134 evaluable patients (68.7%) after a median duration of 2.4 hours (IQR 2.0-3.9). During the 90-day follow up, six patients (4.4%) had a post-reversal thromboembolic event and 20 patients (14.6%) died.

Conclusions

Idarucizumab showed a rapid and complete reversal of dabigatran activity in nearly all patients presenting with GI bleeding, facilitating emergency patient care without the additional presence of anticoagulation.

INTRODUCTION

Dabigatran etexilate (Pradaxa®) is a direct thrombin inhibitor that has a favorable risk-benefit profile compared to vitamin K antagonists (VKA) for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation and treatment of patients with venous thromboembolism (1, 2). Even so, as with all anticoagulants, dabigatran still confers a risk of gastrointestinal (GI) bleeding that in rare cases can lead to hemodynamic instability and result in high risk for morbidity and mortality (3). In patients with non-valvular atrial fibrillation, the 150 mg BID dose of dabigatran was associated with an increased risk of GI bleeding and the 110 mg BID dose was comparable to VKA (1). Thus, an agent that can rapidly counteract the anticoagulant effect of dabigatran in these patients would be a valuable tool in severe bleeding management.

Idarucizumab (Praxbind®) is a humanized monoclonal antibody fragment that binds dabigatran with high affinity, neutralizing its ability to inhibit thrombin (4, 5). In the RE-VERSE AD study, idarucizumab provided rapid, effective, safe, and durable reversal of dabigatran activity in the presence of uncontrollable hemorrhage or the need for urgent surgery (6). Prior to the availability of idarucizumab, treatment and prevention of uncontrollable bleeding in dabigatran-treated patients involved supportive care and non-specific blood products (1, 7, 8). Experience with the use of coagulation factors such as prothrombin complex concentrate (PCC) to antagonize dabigatran activity is limited and its effectiveness has never been studied in clinical trials (9).

In the large RE-VERSE AD study, GI bleeding accounted for 45.5% of all qualifying bleeding events, which was the most frequent organ system location (6). The purpose of the present analysis is to provide insights from RE-VERSE AD regarding the extent of dabigatran reversal, the frequency of full bleeding cessation within the first 24 hours, and occurrence of both thromboembolic events and mortality over a 90-day follow up period in patients reversed for uncontrollable GI bleeding.

METHODS

Study design and population

The RE-VERSE AD study was a prospective, multicenter, open-label cohort evaluation of the efficacy and safety of idarucizumab in the reversal of dabigatran-related anticoagulation. The design and rationale for REVERSE-AD as well as its main results have been published previously (6, 10). Briefly, two dabigatran-treated patient groups were evaluated: Group A comprised patients who had uncontrollable bleeding that was judged by the clinician to warrant acute reversal and Group B consisted of patients who were about to undergo an intervention that could not be delayed for at least 8 hours. Every

patient received intravenous idarucizumab, administered as two 50ml bolus infusions, each containing 2.5g idarucizumab, no more than 15 minutes apart. Patients were classified by the site investigator as having upper or lower GI tract bleeding, defined respectively as bleeding that was presumed to originate from a source proximal or distal to the ligament of Treitz respectively, as diagnosed clinically, by imaging and/or by endoscopic examination as guided by clinical presentation (11). All patients provided written informed consent. The study protocol was approved by all the relevant institutional review boards. The data, analytic methods, and study materials will be made available on request to other researchers for purposes of reproducing the results or replicating the procedure.

Study endpoints and follow-up procedures

The primary endpoint of RE-VERSE AD was the maximum reversal of dabigatran's anticoagulant activity as measured by the diluted thrombin time (dTT) or ecarin clotting time (ECT) within 4 hours after the end of the second infusion of idarucizumab. Complete reversal was achieved if assay results were at or below the upper limit of normal (ULN) for at least one of five time points during the first 4 hours post-idarucizumab infusion. Both the dTT and ECT have previously been shown to correlate to actual dabigatran levels across a wide concentration range (5). The activated partial thrombin time (aPTT, both in local and reference laboratories) was also evaluated as an endpoint in RE-VERSE AD. Since both ECT and aPTT are also subject to greater test variability, the main focus of the present study was the change in dTT. Reversal of ECT and aPTT values was reported in the supplement. The maximum reversal of dabigatran was calculated as follows: percentage reversal = (predose test result [in seconds] – minimum postdose test result [in seconds]) / (predose test result [in seconds] – upper limit of the normal range [in seconds]) × 100%. The ULN of the dTT in the reference laboratory was 36 seconds (10). The minimum postdose test result is the lowest value from the five measurements within four hours. Patients without elevated dTT values were treated with idarucizumab based on clinical necessity and were included in all safety analyses, but were excluded from our primary analysis.

Further endpoints included: 1) time to bleeding cessation, as assessed by the treating physician and defined by stabilization of pulse, blood pressure and/or of hemoglobin values or, if the site was endoscopically evaluable, visible determination, 2) post-reversal re-bleeding and thrombotic events occurring within 90 days of reversal; and 3) death. The extent of bleeding and hemodynamic stability were assessed by the site investigator between 10 and 30 minutes and at 1, 2, 4, 12, and 24 hours after idarucizumab administration, or when considered clinically appropriate. All bleeding events were censored at a maximum duration of 24 +/- 1 hours. Patients were enrolled based on clinical presentation of uncontrolled bleeding that in the opinion of the treating clinician

required immediate reversal of anticoagulation. The severity of bleeding was classified post-hoc using the International Society on Thrombosis and Haemostasis (ISTH) criteria (12). Patients were followed from the time of idarucizumab infusion up to 90 days after the infusion. The occurrence of, any suspected thrombotic events and deaths were recorded and adjudicated by an independent committee. Two patients died outside the protocol-specified 90 day follow up, and are not included in further analyses.

Statistics

Data were analyzed using descriptive statistics expressed as either the mean (standard deviation [SD]) or median (interquartile range [IQR]). For categorical variables, frequencies (n) and percentages (%) were used. The primary endpoint of the maximum dabigatran reversal within 4 hours of idarucizumab administration was only calculated for patients in whom pre-treatment values exceeded the upper limit of the normal range in the central laboratory (6). All analyses were performed using the statistical software SAS version 9.4 (SAS Institute, Cary, N.C).

RESULTS

Patient characteristics

The GI tract was the site of qualifying hemorrhage in 137 of 301 (45.5%) of bleeding patients enrolled in Group A of the REVERSE-AD cohort, representing the commonest organ source of hemorrhage.(6) Of the 137 patients, 43 (31.4%) presented with lower and 48 (35.0%) for upper GI bleeding; four patients (2.9%) had both upper and lower GI bleeding and in 42 patients (30.7%) the bleeding site remained unidentified. Patients' demographics did not differ by location of the GI bleeding. The mean age was 78 years (SD 10) and 75 patients (54.7%) were male. Ninety-one patients (66.4%) were on the 110 mg BID dose. Many patients had additional comorbidities, including 114 (83.2%) with hypertension, 68 (49.6%) with chronic heart failure and 39 (28.5%) with prior stroke or TIA (**Table 1**). Proton pump inhibitors were used at presentation in 38 patients (27.7%) and 20 patients (14.6%) were treated with antiplatelet therapy alongside dabigatran. The median hemoglobin level at baseline was 8.1 g/dL (IQR 6.7-10.1). The patient-reported last dabigatran intake was at a median of 13 hours (IQR 8-20) prior to idarucizumab administration. A total of 121 (88.3%) patients had elevated dTT levels at enrollment with a median of 58 seconds (IQR 44-86). ISTH bleeding was classified as minor in 16% of patients with GI bleeds, however, dabigatran levels, time since the last dabigatran dose and baseline dTT were similar regardless of whether the patients with minor bleeds were included in the cohort or not.

Table 1. Baseline characteristics of 137 patients enrolled with gastrointestinal (GI) bleeding. Data in patients with both upper and lower bleeding are presented as range instead of IQR due to small numbers.

	Anatomic location of bleeding in GI tract				
Clinical characteristic	**Lower (n=43)**	**Upper (n=48)**	**Unknown (n=42)**	**Lower and Upper (n=4)**	**Total (n=137)**
Age (years), mean ± SD	80 ± 7	77 ± 13	79 ± 9	78 ± 7	78 ± 10
Male sex, n (%)	22 (51.1)	28 (58.3)	24 (57.1)	1 (25.0)	75 (54.7)
BMI (kg/m^2)#, mean ± (SD)	27 ± 4.9	27 ± 6.7	29 ± 11.6	27 ± 4.3	28 ± 7.9
Comorbidities, n (%)					
Hypertension	36 (83.7)	37 (77.1)	38 (90.5)	3 (75.0)	114 (83.2)
CHF	19 (44.2)	27 (56.3)	21 (50.0)	1 (25.0)	68 (49.6)
Diabetes	10 (23.3)	18 (37.5)	14 (33.3)	2 (50.0)	44 (32.1)
Prior ischemic stroke/TIA	14 (32.6)	11 (22.9)	13 (31.0)	1 (25.0)	39 (28.5)
Prior major bleeding	3 (7.0)	6 (12.5)	3 (7.1)	0	12 (8.8)
Active cancer	2 (4.7)	7 (14.6)	1 (2.4)	0	10 (7.3)
Creatinine clearance (ml/min)°, median (IQR)	49 (37-63)	49 (29-59)	39 (31-59)	37 (21-65)	46 (31-60)
Hemoglobin level (g/dL)^, median (IQR)	9.5 (7.7-10.4)	7.6 (6.0-10.1)	7.8 (6.7-9.2)	8.1 (4.7-10.5)	8.1 (6.7-10.1)
Bleeding severity (ISTH criteria), n (%)					
Minor	9 (20.9)	8 (16.7)	4 (9.5)	1 (25.0)	22 (16.1)
Major	28 (65.1)	27 (56.3)	26 (61.9)	1 (25.0)	82 (59.9)
Life-threatening	5 (11.6)	12 (25.0)	11 (26.2)	2 (50.0)	30 (21.9)
Not assessable	1 (2.3)	1 (2.1)	1 (2.4)	0	3 (2.2)
Dabigatran dose, n (%)					
150 mg BID	6 (14.0)	14 (29.2)	16 (38.1)	1 (25.0)	37 (27.0)
110 mg BID	35 (81.4)	30 (62.5)	23 (54.8)	3 (75.0)	91 (66.4)
75 mg BID	2 (4.7)	3 (6.3)	3 (7.1)	0	8 (5.8)
Missing	0	1 (2.1)	0	0	1 (0.7)
Time since last dabigatran dose (hours)§, median (IQR)	14 (9-24)	13 (8-17)	13 (7-30)	5 (4-10)	13 (8-20)
Elevated dTT at baseline*, n (%)	41 (95.3)	38 (79.2)	38 (90.5)	4 (100)	121 (88.3)
Baseline dTT (seconds)*, median (IQR)	56 (46-70)	55 (42-86)	65 (42-90)	72 (58-112)	58 (44-86)
Concomitant medication use, n (%)					
Antiplatelet	6 (14.0)	6 (12.5)	7 (16.7)	1 (25.0)	20 (14.6)
NSAID	0	0	1 (2.4)	0	1 (0.7)
Proton Pump Inhibitor	13 (30.2)	12 (25.0)	12 (28.6)	1 (25.0)	38 (27.7)

Note: #7 patients with missing BMI; °3 with missing creatinine clearance; ^2 with missing hemoglobin level; §1 with missing time since last dabigatran dose; *3 with missing dTT at baseline.

GI tract pathology was also recorded at the time of patient enrollment into the study, although this was not mandatory and may represent under-reporting of actual pathology (**Supplement Table 1**). Gastric and duodenal ulcers were common in those with upper GI bleeding (25.0%), whereas polyps and diverticular disease were identified frequently in patients with lower GI bleeding (9.3% and 16.3% respectively). Newly diagnosed luminal GI cancer was reported in at least 2 patients in source documentation, one with a GI stromal tumour and one with pancreatic carcinoma involving the stomach. This information reporting was not mandatory, and may represent under-reporting; it was also not captured in the clinical database.

Dabigatran reversal

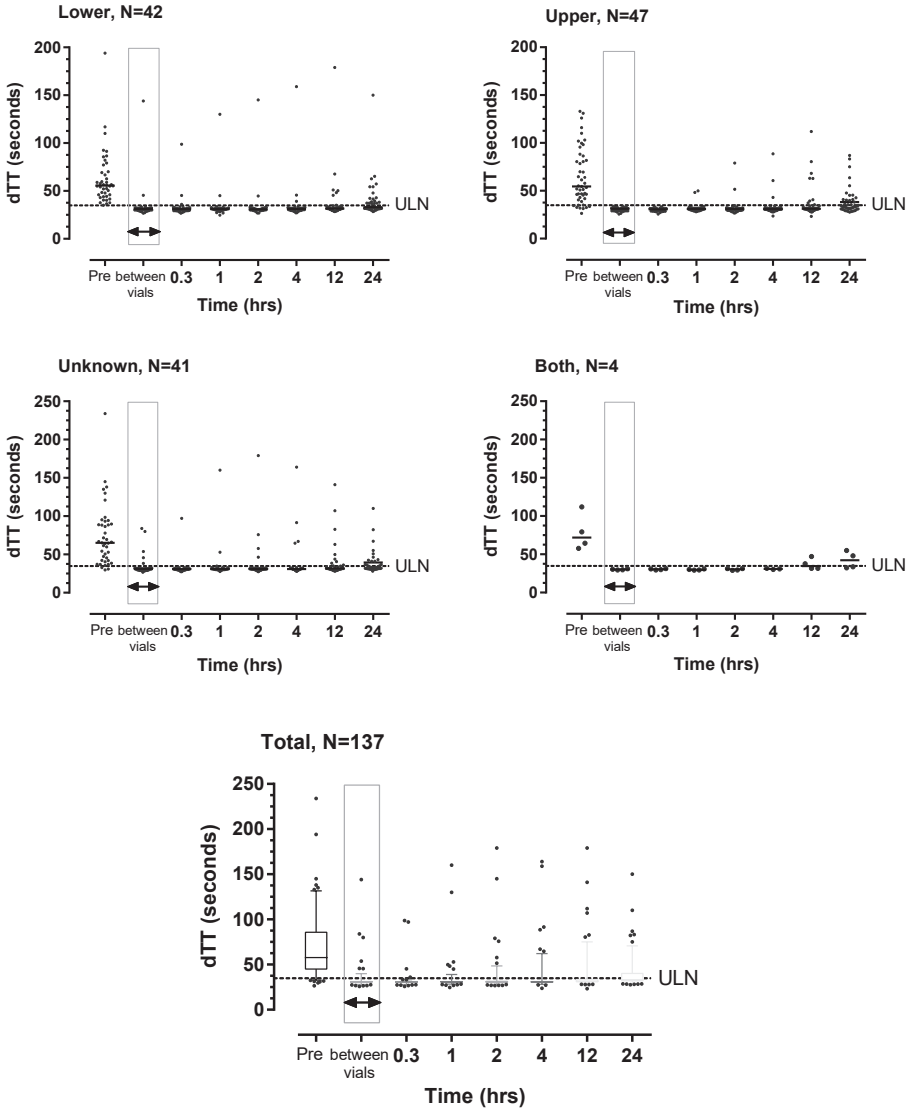
The median time between the start of administering the first vial of idarucizumab to the end of the last vial was 19 minutes (14-25 minutes) in patients with GI bleeding. Complete anticoagulation reversal was observed within 10-30 minutes in 118 of the 121 patients (97.5%) with elevated dTT values at baseline and was similar for all sites of GI bleeding (**Figure 1**). The three patients (2.5%) without complete initial reversal had three to seven fold increased ULN dTT values but still had a reversal effect of at least 50%. This reversal persisted for at least four hours in 110 of 121 patients (90.9%) and up to 24 hours in 71 of 121 patients (58.7%). Extent of reversal using the ECT and (central laboratory) aPTT assays were comparable to reversal with dTT (**Supplement Figure 1 and 2**)**.**

A re-elevation of dTT above ULN occurred in 25 patients (20.7%) within twelve hours and in 50 patients (41.3%) within 24 hours. In 10 of these 50 patients (20.0%) re-bleeding was reported within 48 hours after idarucizumab administration. These 10 re-bleeding patients had higher baseline dTT levels (median 115.5, IQR 79-134, versus 87 seconds, IQR 65-101) as well as higher dTT re-elevation levels at 24 hours (median 66, IQR 54-89, versus 41 seconds, IQR 38-48) compared to the 40 patients with re-elevation but no re-bleeding. Three of these patients also received a second 5g dose of idarucizumab after a re-bleeding episode (**Supplement Figure 3**). These patients had a creatinine clearance at enrollment of 26, 43 and 29 mL/min and dTT at baseline of 133, 79 and 78 seconds. A second dose of idarucizumab was administered between 24 and 48 hours after the first dose, the dTT prior to the second dose was 74, 70 and 55 seconds. Cessation of bleeding occurred in all three patients within an hour and reducing the dTT reversed to below the ULN. Of the 10 patients with re-bleeding, five died, of whom one because of the re-bleeding.

Cessation of Bleeding

In patients with lower GI bleeding, 76.2% were assessable within 24 (+1) hours, with a time of 2.1 hours (1.3-7.9) to bleeding cessation (**Table 2**). Bleeding cessation occurred in 9.5% of patients at time points >25 hours, and could not be confirmed in 14.3% of patients. In the upper GI location, 82.6% were assessable within 24 (+1) hours, with a

Figure 1. Reversal of diluted thrombin time (dTT) after administration of idarucizumab (rectangular box in each graph) in patients with lower or upper gastrointestinal (GI) bleeds or in those with unknown locations or with both upper and lower bleeding. Data points represent individual patients. ULN: upper limit of normal for the dTT is identified as dashed line.



median time of 2.7 (1.5-9.6) hours, 4.3% of patients stopped bleeding >25 hours and 13.0% were not assessable. In patients with an unknown location of GI bleed, 52.4% were assessable within 24 (+1) hours, with a median of 3.2 (2.0-6.5) hours, 14.3% stopped bleeding at times >25 hours and 33.3% were not confirmed. In patients with more than one location, bleeding cessation occurred within 24 (+1) hours in 100% of patients after 6.4 (0.8-16.0) hours.

Table 2. Time to bleeding cessation, number of thrombotic events and mortality in 137 patients with gastrointestinal (GI) bleeding after receiving idarucizumab. Patients could not be evaluated if bleeding stopped prior to idarucizumab (n=1) or there was no post-baseline bleeding assessment possible (n=2).

	Anatomic location of bleeding in GI tract				
	Lower n=43	**Upper n=48**	**Unknown n=42**	**Lower plus Upper n=4**	**Total n=137**
Cessation of Bleeding					
Evaluated patients	42	46	42	4	134
Time to cessation (hrs), median (IQR)	2.0 (1.3-6.4)	2.7 (1.5-8.0)	2.7 (1.9-6.1)	6.4 (0.8-16.0)	2.4 (1.5-6.4)
Patients with Thrombotic Events, n (%)					
0-5 days	0	2 (4.2)	1 (2.4)	0	3 (2.2)
0-30 days	0	2 (4.2)	2 (4.8)	0	4 (2.9)
0-90 days	0	3 (6.3)	3 (7.1)	0	6 (4.4)
Mortality, n (%)					
0-5 days	1 (2.3)	1 (2.1)	3 (7.1)	0	5 (3.6)
0-30 days	3 (7.0)	6 (12.5)	6 (14.3)	0	15 (10.9)
0-90 days	5 (11.6)	7 (14.6)	8 (19.0)	0	20 (14.6)

Blood product management

A total of 117 patients (85.4%) in this cohort also received blood products; 113 (82.5%) received packed red blood cell transfusions and 6 (4.4%) received PCCs, 2 (1.5%) activated PCCs and 1 recombinant activated Factor VII (0.7%; **Table 3**). Administration of these procoagulant agents had no effect on dabigatran reversal by idarucizumab as demonstrated by dTT, ECT and aPTT (data not shown).

Thromboembolic events and anticoagulation resumption

A total of six patients (4.4%) experienced seven thromboembolic events during the 90-day follow up period, of which four occurred within 30 days (2.9%; **Table 2**). Five of these events in four patients occurred in the absence of anticoagulation: one myocardial infarction, one day after first idarucizumab dose, two deep vein thromboses (one with concurrent pulmonary embolism), occurring at two days, and one ischemic stroke, occurring at 35 days post-idarucizumab. Two ischemic strokes occurred 19 and 74 days post-idarucizumab while anticoagulant therapy was restarted (**Table 4**). Overall,

Table 3. The number of patients presenting with gastrointestinal (GI) bleeding who received hemostatic agents both prior to and post idarucizumab treatment. All data is presented as n (%).

Patients receiving blood products	Anatomic location of bleeding in GI tract				
	Lower n=43	Upper n=48	Unknown n=42	Lower plus Upper n=4	Total n=137
Overall	36 (83.7)	41 (85.4)	37 (88.1)	3 (75.0)	117 (85.4)
Blood components					
Packed red blood cells	33 (76.7)	41 (85.4)	36 (85.7)	3 (75.0)	113 (82.5)
Fresh Frozen Plasma	10 (23.3)	14 (29.2)	10 (23.8)	1 (25.0)	35 (25.5)
Platelets	1 (2.3)	2 (4.2)	5 (11.9)	0	8 (5.8)
Cryoprecipitate	1 (2.3)	1 (2.1)	1 (2.4)	0	3 (2.2)
Whole blood	1 (2.3)	0	1 (2.4)	0	2 (1.5)
Coagulation Factor Concentrates					
3 or 4-factor prothrombin complex concentrate (PCC)	3 (7.0)	2 (4.2)	1 (2.4)	0	6 (4.4)
Recombinant activated Factor VII	0	0	1 (2.4)	0	1 (0.7)
Activated prothrombin complex concentrate (aPCC)	1 (2.3)	0	1 (2.4)	0	2 (1.5)
Volume expanders, prohemostatic agents					
Volume expanders	12 (27.9)	10 (20.8)	1 (2.4)	0	23 (16.8)
Tranexamic acid	10 (23.3)	5 (10.4)	10 (23.8)	0	25 (18.2)
Other	0	0	1 (2.4)	0	1 (0.7)

Table 4. Thrombotic events occurring in patients after receiving idarucizumab for management of gastrointestinal (GI) bleeding associated with dabigatran.

Thrombotic event	Anatomic location of GI bleed	Time of adverse event post-idarucizumab* (days)	Time until restart of anticoagulant treatment# (days)		Additional blood products used to manage bleeding
			Parenteral	Dabigatran	
Myocardial infarction	Upper	1	-	6.4	Albumin
Deep venous thrombosis	Upper	2	-	13.7	PRBCs
Pulmonary embolism + deep venous thrombosis	Unknown	2	2	23.5	PRBCs, TxA, FFP
Fatal Ischemic stroke	Unknown	19	5.3	-	PRBCs, FFP, Platelets
Ischemic stroke	Upper	35	35.2	-	PRBCs
Fatal Ischemic stroke	Unknown	74	48.9	55.0	Whole blood

Note: PRBCs=Packed Red Blood Cells, TxA=Tranexamic Acid, FFP=Fresh Frozen Plasma.

48 patients (35.0%) received parenteral anticoagulation during hospitalization and 91 patients (66.4%) restarted some form of oral anticoagulant therapy after a median of 16 days (IQR 7-34; **Supplement Table 2**). In 31 patients (22.6%) dabigatran was resumed after a median of 16 days (IQR 6-38). Overall, patients were discharged from hospital after a median of seven days (IQR 4-12).

Mortality

The 30-day and 90-day mortality was 10.9% (15 patients) and 14.6% (20 patients) respectively (**Table 3**). The median time of death was 18 days (IQR 6-35) post idarucizumab. Causes of death included cardiac failure (four patients), respiratory failure/infection (three patients), myocardial infarction (three patients), hemorrhage (two patients) and, kidney failure, sepsis, electrolyte imbalance, inanition, disseminated intravascular coagulation, ischemic stroke, Parkinson's disease and sudden death (one patient each).

DISCUSSION

The main finding of this post-hoc analysis of the REVERSE-AD study is that idarucizumab showed a rapid and complete reversal of dabigatran activity in 97.5% of patients presenting with GI bleeding who had an elevated diluted thrombin time (dTT) regardless of the GI bleeding location.

This highly efficacious reversal is consistent with the published results of the entire REVERSE-AD study, which included patients with bleeding into other organs and in non-bleeding patients requiring urgent interventions while anticoagulated with dabigatran (6). Overall, reversal was achieved rapidly and persisted up to 24 hours in the majority of patients after one dose of idarucizumab. The rapid and immediate decrease of dTT values demonstrates that reversal of dabigatran is directly related to the administration of idarucizumab and is consistent with its mechanism of action and previous results in healthy volunteers (4, 13). After 24 hours, 50 patients (41.3%) had a re-elevation of dTT values above the ULN. Re-elevation of dabigatran is possibly due to the redistribution of unbound dabigatran from the peripheral tissues to the intravascular compartment over time, since idarucizumab is rapidly cleared (~95% of the dose is cleared 4 hours after administration) (6). Re-elevation of the dTT was associated with re-bleeding in 10 of 50 patients (20%). In general, patients with re-bleeding had a high baseline dTT and higher re-elevated dTT levels at 24 hours. Measurement of anticoagulation in hospitalized patients after a GI bleed may be important for further clinical assessment. If re-bleeding occurs and clotting assays are elevated, then a second dose of idarucizumab may be warranted (14). However, if re-bleeding occurs but clotting assays are not elevated, then re-bleeding is likely anticoagulant independent and should be addressed with bleeding

management procedures. Clinical variables such as blood pressure, effect of the initial intervention and thrombocyte count may also be important contributors to re-bleeding.

A second dose of idarucizumab was administered to three patients with re-bleeding, in whom the dTT reversed to below ULN and re-bleeding stopped promptly within an hour. This illustrates that in rare cases a second dose was indicated to stop the bleeding, which was well tolerated by patients.

The present study provides important information that dabigatran activity was completely reversed in patients presenting with uncontrollable GI bleeding. The frequency of GI bleeding from upper or lower GI tract locations in dabigatran-treated patients was comparable and consistent with previous observations (15, 16). Also, in accordance with earlier findings, the frequency of upper GI bleeding was primarily due to ulceration, whereas lower GI bleeding was frequently associated with diverticulosis and polyps (17, 18). Interestingly, the location of GI bleeding remained unidentified in 31% of the patients. This could be due to a bleeding source within the small intestine at a site beyond the reach of traditional endoscopy or, to delayed or absent diagnostic evaluation.

Overall, 82.5% of the patients received red blood cell transfusions, which was higher than reported by other studies (19, 20). A study performed by Pannach *et al.* (2017), including all major GI bleeding events documented in a prospective non-vitamin K dependent oral anticoagulant (NOAC) registry, found 44% red blood cell transfusions in 143 patients using NOACs (19). In addition, an observational study performed by Yan Xu *et al.* (2017) found this rate to be 52% in 460 NOAC-related bleeding events, which mostly were located in the GI tract (20), who had potentially more serious events than in other studies (12). In the study by Yan Xu *et al.* (2017) PCC and rFVIIa were more frequently used than in our study, possibly because idarucizumab was not available in their study (20). In all cases of major GI bleeding, there is variation among clinicians in identifying and acting upon thresholds for transfusion therapy.

Twenty of 137 patients with an index event of GI bleeding died during the 90-day follow up. This underlines the poor prognosis of the critically ill patients in the present study, of whom many presented with hemodynamic instability and suffered from co-morbidities, despite normalization of coagulation. In addition, the long follow-up of these elderly patients in this study precludes direct comparisons to other studies, where follow-up duration is often shorter. The in-hospital mortality in a study by Pannach *et al.* (2017) was 1.6% in NOAC-treated patients and 5.6% in VKA-treated patients (mean hospital stay, 6.9 and 12.6 days, respectively) (19). Though in-hospital mortality was not recorded in our study, the five day mortality was 3.6%, consistent with these results. Pannach *et al.* (2017) also included patients with controllable GI bleeding, again reflecting the more severely ill patients enrolled in the current study and potentially explaining the higher mortality rate.

The incidence of thromboembolic events after 30 and 90 days was 2.9% and 4.4% respectively, which is comparable with a pooled 2.3% (95%CI 0.5-5.4) incidence reported in patients requiring urgent VKA reversal by PCCs in high quality studies with varying follow up durations (21). Importantly, nearly all thromboembolic events occurred in patients in whom oral anticoagulation had not been restarted. One third of the patients did not resume any form of anticoagulant therapy, consistent with findings of Pannach *et al.* (2017) (19). There is limited evidence to support the decision and timing of resuming anticoagulation after GI bleeding. Current American College of Gastroenterology guidelines do not discuss the resumption of oral anticoagulation after GI bleeding, whereas current European Society of Cardiology guidelines suggest that an oral anticoagulant should be restarted as soon as the thrombotic risk outweighs the bleeding risk, mostly within one week (22, 23). Available scant evidence from VKA experience suggests that the optimal timing to restart oral anticoagulation after a GI bleeding is around 7 to 15 days (24). This is in line with our study in which oral anticoagulation was restarted after a median time of 16 days from the initial GI bleeding event.

Strengths and limitations

This is the first analysis focusing on idarucizumab use in patients with GI bleeding. Because of the pragmatic design of this study, it reflects usual acute clinical care. These data may provide further insights to practicing physicians about the role of idarucizumab in the management of dabigatran-related major GI bleeding.

This study had several limitations. First, a control group is lacking because ethical aspects prohibited the inclusion of a placebo control group in very sick patients with no alternative targeted reversal treatment available (6). Second, the study protocol did not require collection of specific details of diagnostic and interventional endoscopic procedures. Third, details of cessation of bleeding could not always accurately be assessed in non-visible GI bleeding. Nonetheless, the clinical impact of bleeding events was always assessed by the attending physician.

In conclusion, idarucizumab showed a rapid and complete reversal of dabigatran activity in nearly all patients presenting with GI bleeding, regardless of the localisation, and can be safely administered in conjunction with hemostatic agents. Our findings provide relevant further insights to practising physicians on the role of idarucizumab in the management of dabigatran-related major GI bleeding events.

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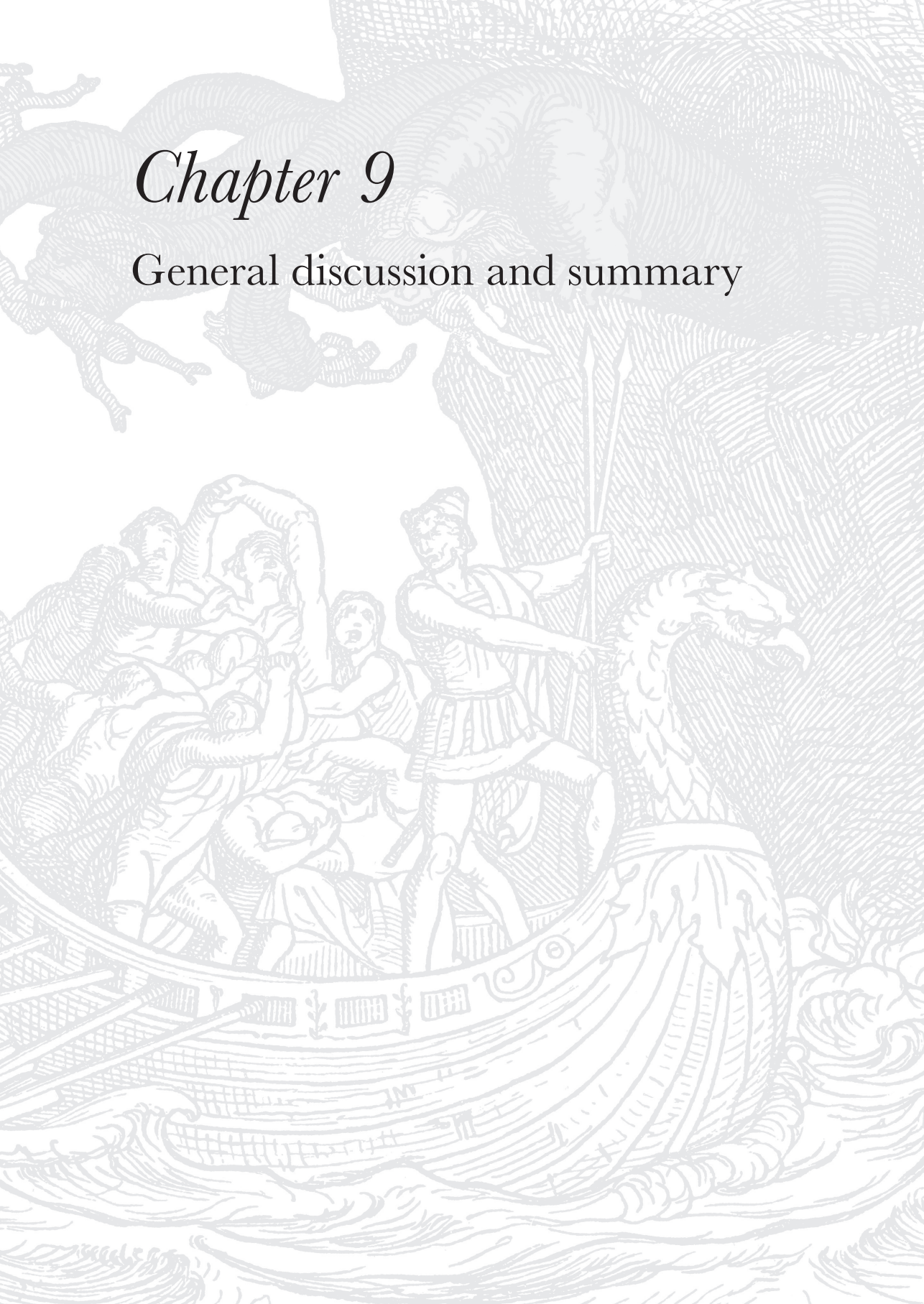

Chapter 9

General discussion and summary

This thesis aimed to evaluate and improve therapeutic anticoagulation strategies in patients presenting with venous thromboembolism (VTE) and to prevent arterial thrombosis after heart valve surgery. In addition, this thesis aimed to establish optimal major bleeding management with idarucizumab for urgent dabigatran reversal. **Chapter 1** comprises a general introduction and overview of the presented studies.

Part I: Venous thromboembolism

Chapter 2 describes the results of a systematic review and meta-analysis on the fatal recurrent VTE risk after anticoagulation discontinuation in patients initially presenting with unprovoked VTE. A total of 8,914 patients were included in 24 high-quality studies. We observed a pooled fatal recurrent VTE fatality rate of 0.13 (95%CI 0.036-0.25) per 100 patient-years with a case-fatality rate of 2.0% (95%CI 0.69-3.8) in studies with high heterogeneity. These findings provide a key missing piece of information on whether or not to prolong anticoagulation treatment in patients with unprovoked VTE beyond the first 3 months. Current guideline recommendations on the duration of treatment of unprovoked VTE would be strengthened if future observational studies show that long-term anticoagulation treatment with direct oral anticoagulants (DOACs) is associated with a rate of fatal bleeding lower than 0.25% per year, representing the upper limit of the 95% confidence interval of the pooled incident rate of fatal recurrent VTE.

The two following chapters address the adherence of daily low-molecular-weight heparin (LMWH) injections in patients with cancer-associated VTE. In **chapter 3**, we evaluated adherence to LMWH therapy during a period of 180 days in 372 patients with cancer-associated VTE. This study demonstrated that one out of five patients with cancer-associated VTE discontinued LMWH treatment during six months, mostly due to unacceptable pain at the injection site. Although this rate may be considered an acceptable trade-off against the reported higher risk of recurrent VTE associated with vitamin K antagonists (VKA), this finding provides relevant background information to current clinical trials investigating the efficacy and safety direct oral anticoagulants (DOACs) compared to LMWH. The oral administration of DOACs might be more practical and patient-friendly than daily subcutaneous LMWH injections. Furthermore, different LMWH compounds might also influence adherence rates. **Chapter 4** revealed that enoxaparin treatment was associated with a higher risk of discontinuation because of side effects compared to nadroparin (hazard ratio 2.8, 95%CI 1.06-7.2). Although further investigation is needed, these findings are relevant for choice of LMWH when treating cancer-associated VTE. DOAC treatment might be an attractive alternative when DOACs are proven non-inferior to LMWH.

Part II: Arterial thrombotic complications after heart valve surgery

After heart valve surgery, patients are at risk of developing systemic arterial thromboembolism. After both bioprosthetic aortic valve implantation and mitral valve repair, the most appropriate antithrombotic therapy is still a subject of controversy. In **Chapter 5**, we aimed to evaluate the rate of thromboembolic and bleeding complications in patients with either acenocoumarol or aspirin therapy after bioprosthetic aortic valve implantation, occurring within one year postoperatively. In this multicenter retrospective study of 402 patients in three Dutch hospitals, acenocoumarol was associated with more bleeding episodes (risk ratio: 8.41, 95%CI 3.58–19.79) and a similar amount of thromboembolic events (risk ratio: 1.2, 95%CI 0.47–3.02) compared with aspirin. This study indicates that aspirin should be favored over acenocoumarol as preferred antithrombotic regimen during the first postoperative year. Similarly, the purpose of **chapter 6** was to compare the rate of thromboembolic and bleeding complications in patients with either vitamin K antagonist (VKA) or aspirin therapy after mitral valve repair. Among 469 patients, no differences were seen in the 3-month cumulative incidence of the combined end point of thromboembolic and bleeding events between aspirin and VKA (hazard ratio: 1.6, 95%CI 0.83-3.1). Moreover, no significant differences were observed in thromboembolic rates (hazard ratio: 0.82, 95%CI 0.16-4.2) as well as in major bleeding rates (hazard ratio: 1.89, 95%CI 0.90-3.9). These findings suggests that the choice of antithrombotic treatment after mitral valve repair should be individualized based on patient-specific considerations, such as risk factors for atrial fibrillation, compliance with treatment and frailty.

Part III: Idarucizumab as antidote of dabigatran

Recently, specific reversal agent idarucizumab (Praxbind®) has been recommended for urgent dabigatran reversal in patients with uncontrolled or life-threatening bleeding or undergoing an emergency procedure. In **chapter 7**, we assessed appropriate usage of idarucizumab in 88 patients which was judged inappropriate in 25 patients (28%). Despite the fact that idarucizumab might optimize urgent management, insufficient knowledge is available about the risk of hypersensitivity and significant drug interactions. Moreover, inappropriate has a negative impact on the healthcare costs. For patients presenting with bleeding, two third achieved effective hemostasis after idarucizumab administration. This proportion was similar to that reported in previous studies evaluating the efficacy of other reversal agents. In line with the large REVERSE-AD trial, we observed a 4.2% rate of thromboembolic and bleeding events, with a mortality rate of 19% within 90 days. This high mortality rate underlines the poor prognosis of the patients enrolled with uncontrollable bleeding or requiring emergency interventions. **Chapter 8** was aimed to provide insights on the efficacy and safety of idarucizumab for urgent dabigatran reversal in patients with major gastrointestinal (GI) bleeding. The GI

tract was the site of qualifying hemorrhage in 137 of 301 (45.5%) of bleeding patients enrolled in Group A of the original REVERSE-AD trial, representing the commonest source of hemorrhage. Idarucizumab was shown to rapidly and completely reverse dabigatran activity in 98% of patients presenting with GI bleeding who had an elevated diluted thrombin time (dTT) regardless of the GI bleeding location. This study confirmed that Idarucizumab is effective for reversal of dabigatran anticoagulation in patients presenting with a major GI bleeding event.

Future perspectives

In the near future, direct oral anticoagulants (DOACs) might not only play an important role in venous thrombosis, but also in preventing arterial thrombosis in patients with stable cardiovascular disease. Currently, antiplatelet therapy is widely used because anticoagulation with vitamin K antagonists (VKAs) - alone or in combination with antiplatelet therapy - was associated with a higher risk of bleeding, including intracranial hemorrhage. A recent study evaluating the efficacy and safety of DOACs in patients with cardiovascular disease reported a lower rate of arterial thrombotic complications of the combination of very low-dose rivaroxaban and aspirin as compared with aspirin monotherapy (1). However, further investigation is evidently needed. Other antiplatelet agents - particularly dual antiplatelet therapy - should have been involved in the study since this combination also was shown to adequately prevent thrombotic complications in this patient category. It would be of great interest to compare the combination of rivaroxaban and aspirin versus $P2Y_{12}$ inhibitor (e.g. ticagrelor) monotherapy and the combination of a $P2Y_{12}$ inhibitor and aspirin. Such a study will probably downsize the promising results of DOACs in preventing arterial thrombosis.

The management of cancer-associated venous thromboembolism (VTE) is also likely to change in the upcoming years. DOACs will be first-line treatment because ongoing trials will probably reveal non-inferiority of DOACs as compared with standard treatment with low-molecular-weight heparin (LMWH), where the oral administration of DOACs is more practical and patient-friendly. However, not all patients with a cancer-associated VTE are candidates for DOAC treatment. DOACs have shown to be associated with more gastrointestinal and abnormal uterine bleeding than VKAs. This suggests that patients with mucosal tumour types might not benefit from DOAC treatment. Although a direct comparison is lacking, apixaban is thought to be associated with less major bleeding than other DOACs. While awaiting the results of the ongoing CARAVAGGIO study (ClinicalTrials.gov Identifier: NCT03045406), apixaban might become an attractive DOAC in this patient category. However, a head-to-head trial would be needed to detect differences between DOACs but it remains to be seen whether such a study will ever be performed. In addition, both DOAC and LMWH treatment are not indicated in patients with end-stage renal failure. In these patients, novel anticoagulation agents may be

of great value. It has been postulated that selective inhibition of intrinsic coagulation factors could provide antithrombotic benefits with low bleeding risk because this will keep the other pathways of coagulation intact for hemostasis. Consequently, factor XI inhibitors have emerged as promising new anticoagulants that may prove to be safer than VKAs or DOACs. The clinical potential of this anticoagulant strategy may represent an exciting new era in anticoagulation, including cancer-associated VTE.

As for the appropriate antithrombotic strategy after bioprosthetic aortic valve implantation and mitral valve repair, future large randomized clinical trials will provide conclusive results about the optimal treatment to prevent arterial and venous thrombotic complications. Although a high number of patients is needed to achieve sufficient power, the ideal study design for both surgical procedures would be to compare three treatment groups: aspirin, VKA and DOAC. Compared with VKA, aspirin and DOAC therapy will likely result in a lower bleeding and similar thrombotic risk. Subsequently, a risk prediction model needs to be developed to select patients who might benefit from either treatment strategies. DOACs might be preferable in patients who, for instance, are at high risk of developing atrial fibrillation postoperatively, whereas aspirin might be favoured in patients without any risk factors or in those with high bleeding risk. Notably, transcatheter aortic valve implantation (TAVI) and a MitraClip will compete with the surgical gold standard. These catheter methods are currently limited to a high-risk patient population with severe valve disease but will likely be increasingly used. A TAVI may require a different antithrombotic approach than a surgical bioprosthetic aortic valve replacement because of a higher risk of valve thrombosis, which is associated with early valve degeneration. Consequently, ongoing trials comparing current treatment standard with dual antiplatelet therapy versus a DOAC and single antiplatelet therapy will possibly show a benefit of DOACs after a TAVI. The appropriate antithrombotic therapy following a MitraClip procedure should be evaluated according to the same study design of ongoing TAVI studies, where antiplatelet monotherapy will likely be sufficient to prevent thrombotic complications.

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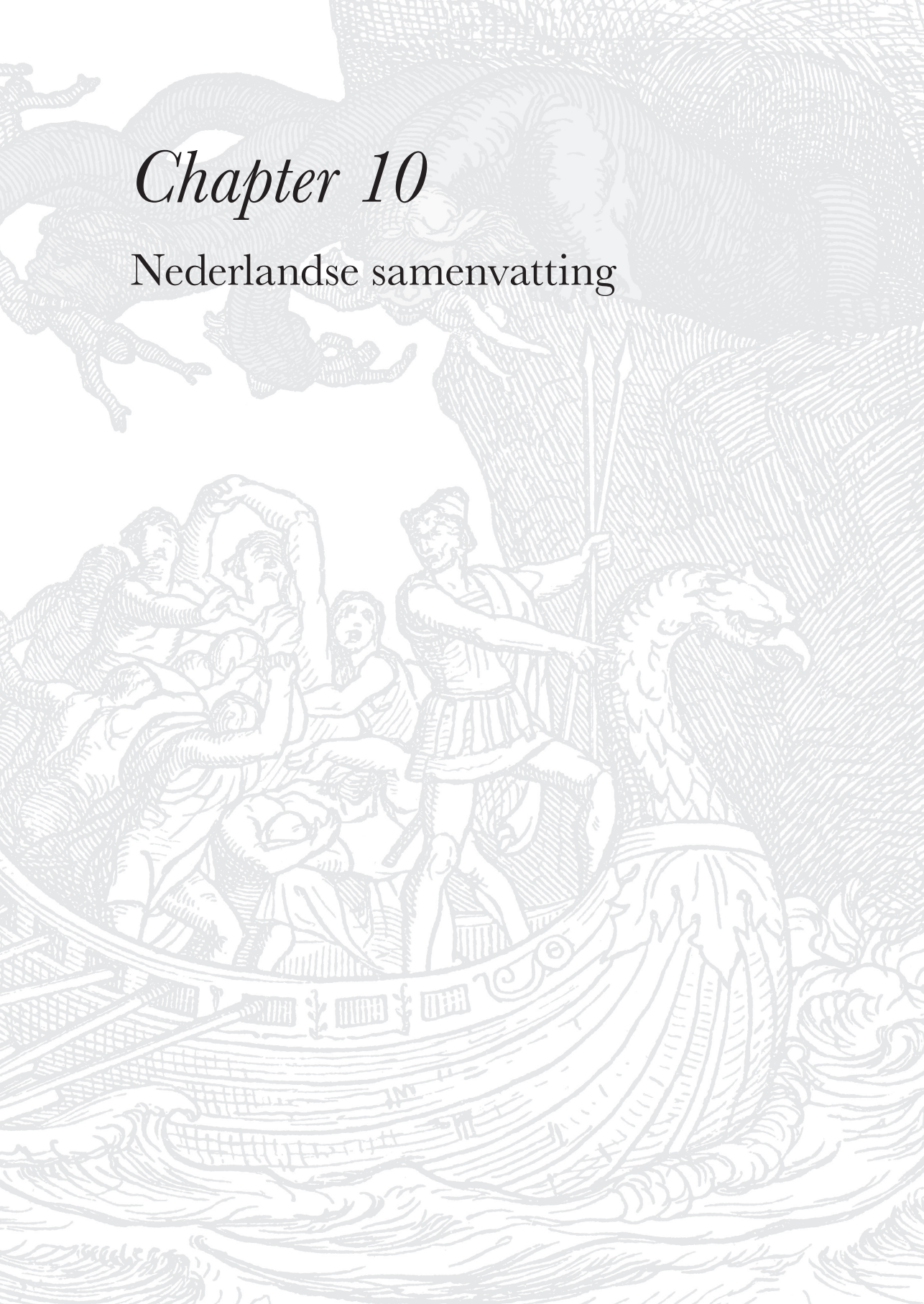

Chapter 10

Nederlandse samenvatting

Dit proefschrift is gericht op het evalueren en verbeteren van antitrombotische behandelstrategieën in patiënten die zich presenteren met een veneuze trombo-embolie (VTE) en die een hartklepoperatie moeten ondergaan om arteriële trombose te voorkomen. Daarnaast bespreekt dit proefschrift zich over de behandeling van dabigatran-gerelateerde majeure bloeding met idarucizumab. **Hoofdstuk 1** is een algemene introductie en overzicht van de beschreven studies in dit proefschrift.

Deel 1: Veneuze trombo-embolie

Hoofdstuk 2 beschrijft de resultaten van een systematische review en meta-analyse waarin het sterfterisico van een recidief VTE na het stoppen van antistollingsbehandeling is onderzocht in patiënten die zich initieel presenteerden met een spontane VTE. In totaal werden 8914 patiënten geïncludeerd in 24 studies van hoge kwaliteit. We observeerden een totaal sterfterisico van 0.13 (95%CI 0.036-0.25) per 100 persoonsjaren dat overeenkwam met een letaliteit van 2.0% (95%CI 0.69-3.8). Deze meta-analyse liet echter belangrijke heterogeniteit tussen de studies zien. Deze bevindingen verstrekken belangrijk informatie over het wel of niet verlengen van antistollingsbehandeling in patiënten met een spontane VTE. Huidige aanbevelingen van richtlijnen over het verlengen van de antistollingsbehandeling bij een spontane VTE worden ondersteund als toekomstige observationele studies aantonen dat langdurige antistollingsbehandeling met direct orale anticoagulantia (DOACs) geassocieerd zijn met een lager fataal bloedingsrisico dan 0.25% per jaar. Dit is de bovengrens van het 95% betrouwbaarheidsinterval van het jaarlijkse sterfterisico aan een recidief VTE.

De twee daaropvolgende hoofdstukken hebben betrekking op het stoppen van dagelijkse subcutane injecties met laag-moleculair-gewicht heparine (LMWH) in patiënten met een kanker-geassocieerde VTE. In **hoofdstuk 3** werd het stoppen van LMWH therapie geëvalueerd in een periode van 180 dagen in 372 patiënten met een kanker-geassocieerde VTE. Deze studie toonde aan dat een op de vijf patiënten was gestopt, meestal door ondragelijke pijn bij de injectieplek. Bovendien hebben verschillende LMWH samenstellingen mogelijk invloed op het risico om te stoppen. **Hoofdstuk 4** liet zien dat de behandeling met enoxaparine geassocieerd is met een hoger risico om te stoppen dan de behandeling met nadroparine (hazard ratio 2.8, 95%CI 1.06-7.2). Deze bevindingen zijn relevant voor de keuze tussen verschillende LMWHs bij de behandeling van kanker-geassocieerde VTE. De orale inname van DOACs blijft echter een aantrekkelijk alternatief als deze inderdaad non-inferieur blijken te zijn aan LMWH.

Deel 2: Arteriële trombotische complicaties na hartklepoperaties

Na een hartklepoperatie hebben patiënten een verhoogd risico op het ontwikkelen van arteriële trombo-embolieën. Hoewel alle patiënten met mechanische kunstkleppen levenslange antistollingsbehandeling nodig hebben, is dit na een biologisch

aortaklepvervanging en mitralisklepreparatie nog steeds omstreden. In **hoofdstuk 5**, beschrijven wij het risico op trombo-embolische en bloedingscomplicaties in patiënten die gedurende een jaar werden behandeld met ofwel acenocoumarol of aspirine na een biologische aortaklepvervanging. In deze retrospectieve studie van 402 patiënten in drie Nederlandse ziekenhuizen was acenocoumarol geassocieerd met meer bloedingscomplicaties (risk ratio: 8.41, 95%CI 3.58–19.79) en een gelijk aantal trombo-embolieën (risk ratio: 1.2, 95%CI 0.47–3.02) als aspirine. Deze studie geeft aan dat aspirine wellicht de voorkeur zou moeten krijgen boven acenocoumarol voor deze indicatie. **Hoofdstuk 6** gaat ook over het vergelijken van de trombo-embolische en bloedingscomplicaties tussen een behandeling met vitamine K antagonisten (VKA) en aspirine, maar in dit geval na een mitralisklepreparatie. In 469 patiënten werd geen verschil gevonden in de cumulatieve incidentie van een gecombineerd eindpunt van trombo-embolische en bloedingscomplicaties na 3 maanden (hazard ratio: 1.6, 95%CI 0.83-3.1). Bovendien waren het trombo-embolisch risico (hazard ratio: 0.82, 95%CI 0.16-4.2) en het bloedingsrisico (hazard ratio: 1.89, 95%CI 0.90-3.9) gelijk in beide behandelgroepen. Deze bevindingen suggereren dat de antitrombotische behandeling na een mitralisklepreparatie geïndividualiseerd moet worden op basis van patiënt-specifieke eigenschappen, zoals (risicofactoren voor) atriumfibrilleren, therapietrouw en kwetsbaarheid.

Deel 3: Idarucizumab als antidotum van dabigatran

Sinds enige tijd is het specifieke antidotum idarucizumab beschikbaar voor het acuut couperen van dabigatran in patiënten met een onbedwingbare of levensbedreigende bloeding, of in patiënten die een spoedinterventie moeten ondergaan. In **hoofdstuk 7** onderzochten wij adequaat gebruik van idarucizumab. In deze observationele multicenter studie includeerden wij 88 patenten in 12 Nederlands ziekenhuizen: 53 patiënten die zich presenteerden met een bloeding en 35 patiënten die een spoedinterventie ondergingen. Wij observeerden onrechtmatig gebruik van idarucizumab in 28% van de patiënten. Ondanks het feit dat idarucizumab de prognose van patiënten in een acute setting kan verbeteren is er weinig bekend over hypersensitiviteit en interacties met andere medicijnen. Tevens heeft het mogelijk een negatieve impact op de kosten van de gezondheidszorg. In de groep patiënten met een bloeding bereikte twee-derde een effectieve hemostase na toediening van idarucizumab. Deze proportie is gelijk aan voorgaande studies die de effectiviteit van andere antidota hebben geëvalueerd. In overeenstemming met de grote RE-VERSE AD studie was het risico op trombo-embolische en bloedingscomplicaties 4.2%, en de sterfte 19% gedurende de 90 dagen dat patiënten gevolgd werden. Deze hoge mortaliteit onderstreept de slechte prognose van patiënten die antistolling gebruiken maar een bloeding krijgen of een spoedinterventie moeten ondergaan, zelfs als het antistollingseffect snel ongedaan kan worden gemaakt. **Hoofdstuk 8** was gericht om inzicht te geven in de effectiviteit en veiligheid van idarucizumab

in patiënten met majeure gastro-intestinale bloedingen tijdens behandeling met dabigatran. Dit betrof een sub-analyse van 137 van de 301 patiënten die geïncludeerd waren in de bloedingsgroep van de originele RE-VERSE AD studie. Daarmee was dit de meest voorkomende bloedingslocatie. Idarucizumab toonde snelle en complete neutralisatie van dabigatran activiteit in 98% van de patiënten die bij binnenkomst in het ziekenhuis een verhoogde verdunde trombine tijd (dTT) hadden als teken van dabigatran activiteit, ongeacht de gastro-intestinale bloedingslocatie. Deze studie bevestigde dat idarucizumab effectief is in het neutraliseren van dabigatran in patiënten die zich presenteren met een majeure gastro-intestinale bloeding.

Toekomstperspectief

In de nabije toekomst zullen directe orale anticoagulantia (DOACs) mogelijk niet alleen een belangrijke rol spelen bij veneuze trombose, maar ook in het voorkomen van arteriële trombose in patiënten met stabiel cardiovasculair vaatlijden. Momenteel wordt plaatjesaggregatieremming ingezet als secundaire cardiovasculaire preventie omdat antistolling met vitamine K antagonisten (VKAs) – alleen of in combinatie met plaatjesaggregatieremming – geassocieerd was met een hoger risico op bloedingen, inclusief intracraniële bloedingen. Een recente studie die de effectiviteit en veiligheid van DOACs heeft onderzocht in patiënten met cardiovasculair vaatlijden toonde een lager risico op arteriële trombotische complicaties bij een behandelcombinatie van een zeer lage dosis rivaroxaban en aspirine dan bij een behandeling met alleen aspirine (1). Echter, meer onderzoek is vereist om de waarde van deze behandeltherapie goed in te kunnen schatten. Andere plaatjesaggregatieremmers – vooral dubbele plaatjesaggregatieremming – hadden bij de studie betrokken moeten worden omdat ook deze effectief zijn in het voorkomen van trombotische complicaties. Het zou daarom zeer relevant zijn om de combinatie van rivaroxaban en aspirine te vergelijken met een $P2Y_{12}$ remmer (bijvoorbeeld ticagrelor) en de combinatie van een $P2Y_{12}$ remmer en aspirine. Een dergelijke studie zal de veelbelovende resultaten van DOACs in het voorkomen van arteriële trombose mogelijk afzwakken.

De behandelstrategie van een kanker-geassocieerde veneuze trombo-embolie (VTE) zal de komende jaren veranderen. DOACs worden waarschijnlijk eerste keus behandeling gezien de huidige studies non-inferioriteit van DOACs ten opzichte van de standaardbehandeling met laag-moleculair-gewicht heparine (LMWH) suggereren, waarbij de orale inname van DOACs praktischer en patiëntvriendelijker is. Niet elke patiënt heeft echter baat bij een behandeling met een DOAC. DOACs zijn geassocieerd met een hoger risico op gastro-intestinale en abnormale uterine bloedingen dan VKAs. Dit suggereert dat DOACs mogelijk vermeden moeten worden in patiënten met mucosale tumoren. Hoewel een directe vergelijking ontbreekt, is apixaban mogelijk geassocieerd met minder majeure bloedingen dan andere DOACs. Of dit ook in de setting van kanker gerelateerde

trombose geldt moet worden afgewacht. Momenteel wordt de CARAVAGGIO studie (ClinicalTrials.gov Identifier: NCT03045406), uitgevoerd, waarbij apixaban wordt vergeleken met dalteparine bij de behandeling van kanker-gerelateerde VTE. Echter, een rechtstreeks vergelijkende studie zal uitgevoerd moeten worden om verschillen tussen DOACs aan te tonen. Het blijft de vraag of een dergelijke studie ooit zal worden uitgevoerd. Tevens is een behandeling met DOAC en LMWH niet geïndiceerd in patiënten met eindstadium nierfalen. In deze patiënten kunnen nieuwe anticoagulantia een goede uitkomst bieden. Momenteel wordt verondersteld dat specifieke remming van de intrinsieke stollingscascade een antitrombotisch voordeel zou kunnen opleveren met een lager een bloedingsrisico omdat andere onderdelen van de stollingscascade intact blijven voor het behouden van hemostase. Daarom wordt de werking van factor XI remmers onderzocht als veelbelovende nieuwe antistollingsmiddelen die mogelijk veiliger zijn dan VKAs of DOACs. Het potentieel van deze antistollingsstrategie luidt mogelijk een nieuw tijdperk in van nieuwe antistolling strategieën, ook bij de behandeling van een kankergeassocieerde VTE.

Wat betreft de antitrombotische strategie na een biologische aortaklepvervanging en een mitralisklepreparatie zullen grote gerandomiseerde trials duidelijkheid moeten verschaffen over de optimale behandeling om arteriële en veneuze trombose te voorkomen. Hoewel een groot aantal patiënten vereist is om goede conclusies te kunnen trekken, zullen na beide procedures idealiter drie behandelgroepen moeten worden vergeleken: aspirine, VKA en DOAC. In vergelijking met de VKA, resulteren aspirine en DOACs waarschijnlijk in een lager bloedings- en gelijk trombo-embolisch risico. Vervolgens zal een predictiemodel ontwikkeld moeten worden ontwikkeld die patiënten selecteert die baat hebben bij één van beide behandelstrategieën. Een DOAC geniet mogelijk de voorkeur in patiënten met een hoogrisico op het ontwikkelen van atriumfibrilleren, waar aspirine adequaat is in patiënten zonder risicofactoren of in diegenen met een hoog bloedingsrisico. Bovendien is het mogelijk dat de minder invasieve transkatheter aortaklepvervanging (TAVI) en MitraClip procedures in de plaats komen van de chirurgische behandeling. Deze transkatheter procedures worden momenteel alleen nog maar verricht in hoogrisico patiëntengroep met ernstige klepziekten, maar zullen naar verwachting toenemen in andere patiëntcategorieën. Een TAVI vereist mogelijk een andere antitrombotische strategie dan een chirurgische biologische aortaklepvervanging wegens een hoger risico op kleptrombose, dat geassocieerd is met vroegtijdige klepdegeneratie. Derhalve zullen lopende studies, die de huidige standaardbehandeling met dubbele plaatjesaggregatieremming vergelijkt met een DOAC en enkele plaatjesaggregatieremming, mogelijk een voordeel aantonen van een behandeling met DOACs. Het optimale antitrombotische beleid na een MitraClip procedure zal moeten worden geëvalueerd volgens eenzelfde onderzoeksopzet als de lopende TAVI studies, waarin plaatjesaggregatieremming waarschijnlijk voldoende beschermt tegen het optreden van trombose.

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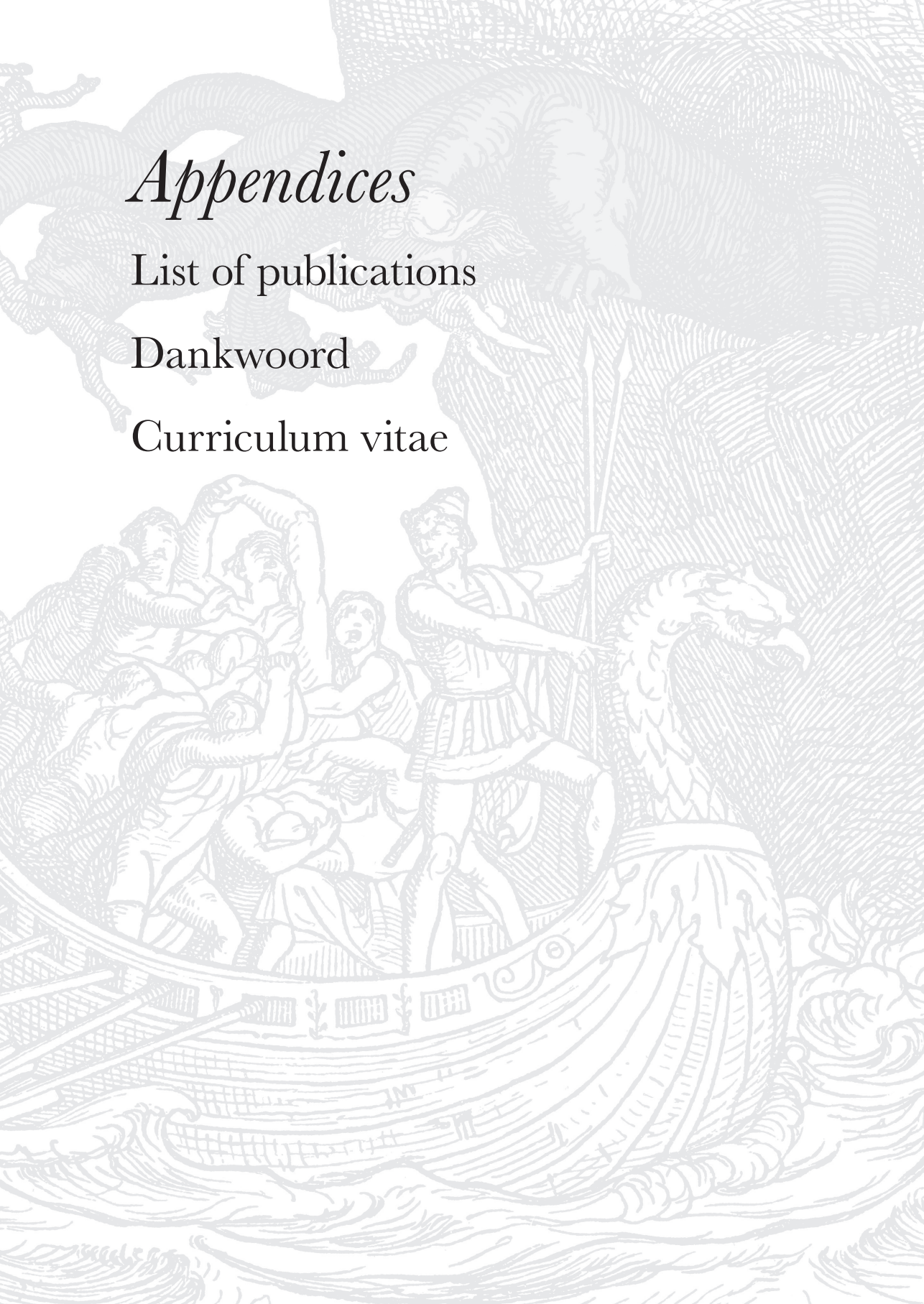

Appendices

List of publications

Dankwoord

Curriculum vitae

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CURRICULUM VITAE

Sake Johannes van der Wall werd geboren op 1 februari 1991 te Amsterdam. In 2009 haalde hij zijn VWO diploma aan het Vossius Gymnasium te Amsterdam. Na een jaar de studie biomedische wetenschappen aan de Universiteit van Amsterdam te hebben gevolgd, startte hij in 2010 met de studie Geneeskunde aan de Universiteit Leiden. Tijdens zijn wetenschapsstage verrichtte hij onderzoek naar antistolling na biologische aortaklepvervangingen op de afdeling Trombose en Hemostase onder leiding van prof. dr. Huisman. In 2015 vingen zijn coschappen aan. Na het behalen van zijn artsexamen in december 2016 zette hij het wetenschappelijk onderzoek op het gebied van antistolling als promovendus voort. De resultaten van zijn promotietraject zijn beschreven in dit proefschrift.