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SPECIAL ARTICLE

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

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ABSTRACT

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

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

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

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

KEYWORDS

Guideline adherence, bleeding, thrombosis, anticoagulants, risk factors for bleeding

INTRODUCTION

Perioperative interruption of chronic anticoagulation harbours the risk of thromboembolism (TE). To minimise the risk of TE during the anticoagulant-free interval, bridging therapy with low-molecular-weight heparins (LMWH) is applied. This introduces the risk of bleeding. Vitamin K antagonists (VKA) are administered to patients at increased risk of a venous or arterial TE due to, for instance, venous thromboembolism, atrial fibrillation, mechanical heart valves, or stroke. According to current guidelines, LMWH or unfractionated heparin (UFH) in therapeutic dosages is the preferred anticoagulant for high TE risk patients undergoing high bleeding risk surgery. For patients with an intermediate TE risk profile two options are available: therapeutic or prophylactic dosages of LMWH. For patients at low TE risk again two options are available: prophylactic dosages or interruption of VKA without LMWH or UFH. In low bleeding risk procedures VKA should not be interrupted. The perioperative administration of UFH or LMWH as a part of bridging therapy possibly leads to increased bleeding risk associated with sometimes severe consequences such as intracranial bleeding with major disability or even death as a result.[1-4] Although guidelines characterise patients at risk and advise on strategies to be followed, the application of bridging therapy is often guideline discordant. Literature reveals that a wide range of approaches to bridging anticoagulation are in use, possibly due to unfamiliarity with the current guidelines and the weak evidence on which they are based.[5,6] Evidence from randomised trials

is lacking, probably because ethical issues might arise during the design of such a study; available evidence is therefore mainly based on observational studies. The incidence of postoperative total bleeding ranges from 4.1 to 25% in populations subject to diverse bridging regimes undergoing different surgical interventions.[4,7-9] The incidence of TE ranges from 0 to 2.6% in different studies.[3,4,10-13] Apart from improvement of adherence to guidelines there is a need for defining patient and procedure-related characteristics which might fine-tune the bridging strategy and thereby decrease the incidence of periprocedural bleeding and TE. Until now, renal insufficiency,[1,14] $CHADS_2$ (a composite score of congestive heart failure, hypertension, age, diabetes and stroke),[8,9,13] mitral valve replacement,[4,15,16] thrombocytopenia,[8,16] LMWH administration within 24 hours after the procedure,[16,17] increasing age,[7,13] and total duration of periprocedural heparin use[18] are the only consistent risk factors for bleeding. Baseline INR in bridging groups is not associated with postoperative bleeding in different studies.[7,19] It is still unclear if the application of bridging therapy results in decreased TE risk when compared with VKA cessation alone or VKA continuation without the administration of LMWH.[20]

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

METHODS

Cohort

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

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

Guideline adherence

We determined guideline adherence of bridging episodes; we ascertained the proportion of patients bridged according to the ACCP guidelines for perioperative management of antithrombotic therapy 2008.[22] These guidelines are officially adopted and propagated in the MUMC+. For surgical bleeding risk classification we made use of a two-tier distribution in our descriptive analyses; dental procedures, (extraction of 1-3 teeth, implant placement, surgical extraction of wisdom teeth, surgical root canal treatment, incision of an abscess, and dental hygiene treatment), cataract surgery, small dermatological interventions, and all other procedures with local anticoagulant options were considered low bleeding risk procedures making it possible to continue VKA treatment. All other procedures were qualified as high bleeding risk procedures and therefore warranted bridging anticoagulation according to ACCP guidelines, providing elevated TE risk was established in the patient. Arterial and venous TE risks were defined as low, intermediate, or high. TE risk in general was defined as a composite score of venous and arterial TE risk. A low, intermediate, or high arterial/venous TE risk was defined as a low, intermediate, or high composite risk respectively; in case of exposure to both an arterial and venous risk the highest score on either risk was expressed as the TE risk. The variable TE risk in general was composed to be able to estimate the combined effect of arterial and venous TE risk on the physician's decision to administer therapeutic doses of LMWH and on bleeding risk in our univariable and multivariable analyses. Guideline adherence was defined as low TE risk patients receiving prophylactic doses of LMWH postprocedurally and intermediate to high TE risk patients receiving prophylactic or therapeutic doses postprocedurally. Patients without prior surgical bleeding undergoing low-risk dental, cataract, or dermatological procedures should not be bridged; continuation of VKA is the preferred option, but for patients who have experienced prior surgical bleeding, bridging is indicated for these low-risk procedures. The period of postoperative administration of LMWH should not exceed seven days. We determined the proportion of all patients on long-term acenocoumarol or phenprocoumon therapy, treated within our institution, who received

postprocedural therapeutic doses of LMWH. In the literature this proportion ranges from 22 to 85% and is associated with major bleeding.[6]

Complications

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

Risk factors for bleeding

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

Statistical analysis

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

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

RESULTS

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

Baseline characteristics

Baseline clinical characteristics are detailed in *table 1*. The average age was 70.3 years (standard deviation (SD) 11.4) and 59.0% were male. Arterial TE risk was the indication for VKA use in 190 patients (85.6%); low-risk atrial fibrillation (AF) with $CHADS_2$ scores 0-1 was the most prevalent condition in 67/190 patients (35.3%). VTE risk was present in 42 patients (18.9%); the most prevalent condition was VTE more than six months ago: 32/42 (76.2%). Ten patients had both an arterial and venous indication for VKA therapy. Creatinine clearance was decreased (≤60 ml/min) in 62/222 (27.9%) of the patients and in 62/126 (49.2%) of the measurements performed. In 96 (43.2%) patients no periprocedural creatinine clearance was determined.

Procedure characteristics

Procedure characteristics are detailed in *table 1*; 222 procedures were performed in 181 patients. In 62 (27.9%) of all cases, bridging therapy was applied for a procedure for which bridging was not indicated; all were low-risk dental, cataract, or dermatological interventions. A variety of inpatient and outpatient procedures were performed: dental procedures, gastroscopies, and colonoscopies were the most prevalent interventions (*table 2*). The majority (143, 64.4%) of all procedures were classified as minimal

Table 1. *Baseline and procedure characteristics, anticoagulation and complications*

Baseline characteristics		
Men		131 (59.0%)
Age (years)		70.3±11.4
Arterial TE risk (n=190)	High	42 (27.4%)
	Intermediate	56 (29.5%)
	Low	80 (42.1%)
	Not mentioned in ACCP/CBO guidelines	12 (6.3%)
Venous TE risk (n=42)	High	9 (21.4%)
	Intermediate	1 (2.4%)
	Low	32 (76.2%)
Creatinine clearance (n=222)	>60 ml/min	64 (28.8%)
	41-60 ml/min	42 (18.9%)
	≤40 ml/min	20 (9.0%)
	No measurement performed	96 (43.2%)
Procedure characteristics		
Bleeding risk procedures ACCP (n=222)	High	160 (72.1%)
	High bleeding risk procedure	157 (70.7%)
	Bleeding previous surgery	3 (1.4%)
	Low	62 (27.9%)
	Low bleeding risk procedure	62 (27.9%)
Bleeding risk 5-point scale (n=222)	Score 1	143 (64.4%)
	Score 2	33 (14.9%)
	Score 3	39 (17.6%)
	Score 4	7 (3.2%)
	Score 5	0 (0.0%)
Anticoagulation characteristics		
VKA (n=222)	Acenocoumarol Phenprocoumon	200 (90.1%) 22 (9.9%)
Vitamin K preprocedural (n=6)	Acenocoumarol Phenprocoumon	0 (0.0%) 6 (100%)
LMWH postprocedural (n=222)	Prophylactic	23 (10.4%)
	Therapeutic	199 (89.6%)
Stop time VKA (days)	Acenocoumarol Phenprocoumon	-3.4±1.6 Median: -3.0 -5.3±3.6 Median: -5.0
Restart time VKA postprocedural (days)	Acenocoumarol Phenprocoumon	1.4±3.3 Median: 0.0 2.1±8.0 Median: 0.0
Start time LMWH preprocedural (days)	Acenocoumarol Phenprocoumon	-3.2±1.7 Median: -3.0 -6.3±5.1 Median: -4.0
Stop time LMWH preprocedural (days)	Acenocoumarol Phenprocoumon	-0.9±0.5 Median: -1.0 -1.3±0.6 Median: -1.0
Restart time LMWH postprocedural (hours)	Acenocoumarol Phenprocoumon	19.3±9.9 Median: 24.0 19.3±9.5 Median: 12.0
Anticoagulation characteristics		
Stop time LMWH postprocedural (days)	Acenocoumarol Phenprocoumon	9.6±6.0 Median: 8.0 13.9±11.9 Median: 10.0
Total duration LMWH (days)	Acenocoumarol Phenprocoumon	11.2±6.2 Median: 8.5 17.6±13.8 Median: 13.0
INR day intervention	Acenocoumarol Phenprocoumon	1.1±0.1 1.2±0.2
Time INR>2 (days)	Acenocoumarol Phenprocoumon	8.7±6.9 Median: 7.0 11.8±10.5 Median: 8.0
Low TE risk and postprocedural LMWH dosage		
Low TE risk (n=102) and prophylactic dose		16 (15.7%)
Low TE risk (n=102) and therapeutic dose		86 (84.3%)
Complications		
Bleeding (n=44)	Transfusion	4 (1.8%)
	Hospital treatment	21 (9.5%)
	Minor	19 (8.6%)
TE (n=2)		2 (0.9%)

ACCP = American College of Chest Physicians; AF = atrial fibrillation; CBO = Centraal BegeleidingsOrgaan voor de intercollegiale toetsing; $CHADS_2$ = congestive heart failure, hypertension, age, diabetes and stroke(2); INR = international normalised ratio; LMWH = low-molecular-weight heparin; MHV = mechanical heart valve; TE = thromboembolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.

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

Anticoagulation

Anticoagulation characteristics are detailed in *table 1*. The majority of the patients used acenocoumarol as oral anticoagulant: 200 (90.1 %), the remaining 22 (9.9%) used phenprocoumon. The median preoperative stop time of VKA was day -3 (mean -3.4, SD 1.6) and day -5 (mean -5.3, SD 3.6) for acenocoumarol and phenprocoumon, respectively. Vitamin K was used to reverse anticoagulation only in six patients (2.7%); all used phenprocoumon, a VKA with a relatively long half-life of 120-200 hours. Acenocoumarol was resumed after a median of 0 days (mean 1.4, SD 1.6); phenprocoumon was resumed after a median of 0 days (mean 2.1, SD 8.0). LMWH was used as bridging agent of first choice in all patients. The proportion of patients at low TE risk (n=102) treated with therapeutic doses of LMWH postprocedurally was 84.3% (n=86). We also explored periprocedural timing of LMWH administration; LMWH therapy was initiated at

Table 2. *Procedures performed (n=222)*

Gastrointestinal	
Endoscopy colon/duodenum with or without biopsy	26
Cholecystectomy	2
Abdominal surgery	7
Haemorrhoids	3
Colon polyp removal	1
Orthopaedic	
Total hip arthroplasty	5
Total knee arthroplasty	4
Intra-articular injections	3
Elbow/foot/shoulder surgery	3
Other	8
Urology	
Prostate biopsy	7
TUR prostate	4
Bladder cancer surgery	3
Brachytherapy	2
Kidney scope procedure	5
Cystoscopy with or without biopsy	2
Other	7
Dental	
Extractions	37
Implants	10
Dental hygiene treatment	1
Neurosurgical	
Surgery for spinal disc herniation	5
Lumbar puncture	1
Vascular	
Varices	2
Angioplasty/stent placement	2
Bypass surgery	1
Plastic	
Hand surgery	6
Dermatological procedure	8
Entropion surgery	3
Other	3
Interventional radiology	
Heart biopsy	2
Cardiac catheterisation	9
Other	2
Other	
ENT surgery	2
Neurolysis	11
Cataract	2
Umbilical or inguinal hernia	4
Breast cancer	4
Breast biopsy	6
Bronchoscopy with or without biopsy	4
Other	5

ENT = ear, nose and throat; TUR = transurethral resection of the prostate.

a median of 3 days (mean 3.2, SD 1.7) and a median of 4 days (mean 6.3, SD 5.1) before and stopped a median of 1 (mean 0.9, SD 0.5 and mean 1.3, SD 0.6) day prior to the planned procedure in acenocoumarol and phenprocoumon users, respectively. The median time of postoperative restart of LMWH therapy was 24 hours (mean 19.3, SD 9.9) and 12 hours (mean 19.3, SD 9.5) in acenocoumarol and phenprocoumon users, respectively. The median duration of postoperative LMWH administration was 8 days (mean 11.2, SD 6.2) and 13 days (mean: 17.6, SD 13.8) in acenocoumarol and phenprocoumon users, respectively. Of all patients undergoing bridging therapy, 199 (89.6%) were treated with therapeutic dosages of LMWH after the procedure.

Univariable logistic regression with postprocedural therapeutic dosage of LMWH as the outcome resulted in non-significant effects for all variables. No proof was found that the prescribing physician's decision to administer therapeutic dosages of LMWHs was influenced by age, TE risk, surgical bleeding risk, or creatinine clearance. Patients at high TE risk compared with low-risk patients had a non-significant higher risk of exposure to therapeutic doses (OR 4.22, 95% CI 0.93 to 19.24), p for linear trend=0.06. Patients with a creatinine clearance within the range of 41-60 ml/min compared with a clearance >60 ml/min had a non-significant lower risk of exposure to therapeutic doses (OR 0.43, 95% CI 0.10 to 1.82), p for linear trend=0.88. A high bleeding risk procedure (score 4) on the Jaffer scale compared with a procedure score of 1 resulted in a non-significant decreased risk of exposure to therapeutic doses of LMWH (OR 0.24, 95% CI 0.04 to 1.36), p for linear trend=0.11. Multivariable analyses including the aforementioned variables resulted in overall non-significant results. Patients at high TE risk compared with low risk had a borderline non-significant higher risk of exposure to therapeutic dosages after their intervention (OR 4.96, 95% CI 0.97 to 25.26), p for linear trend=0.05. Patients with a creatinine clearance within the range of 41-60 ml/min compared with clearance >60 ml/min had a non-significant lower risk of exposure to therapeutic doses (OR 0.38, 95% CI 0.08 to 1.81), p for trend=0.73. Finally, a bleeding risk score 4 compared with score 1 resulted in a non-significant decreased risk (OR 0.27, 95% CI 0.04 to 1.86), p for linear trend=0.23. The goodness of fit of the model was assessed, resulting in a p-value of 0.77 on the Hosmer-Lemeshov test and the model chi-square statistic resulted in a p-value of 0.75.

Complications

The 30-day incidence of total bleeding in the entire group of procedures performed was 44 (19.8%), the incidence of major bleeding 25 (11.3%); there were no deaths, no intracranial bleeding, four patients required a transfusion,

and 21 had to be treated in a hospital due to postoperative bleeding. Two patients (0.9%) experienced a deep venous thrombosis and recovered (*table 1*).

Risk factors for bleeding

Univariable logistic regression analysis revealed high versus low TE risk (OR 2.59, 95% CI 1.11 to 6.04), p for linear trend=0.03 and dental procedures (OR 2.98, 95% CI 1.45 to 6.13) as risk factors for total bleeding; all other results are non-significant. Creatinine clearance ≤40 versus >60 ml/min and intermediate versus low TE risk resulted in non-significant elevated risks: OR 2.35, 95% (CI 0.93 to 5.90), p for linear trend=0.07 and OR 1.83, 95% CI 0.77 to 4.33, respectively. To minimise the risk of reversed causality we excluded 18 cases in which VKA were stopped and LMWH administration due to total bleeding was prolonged; the initial significantly increased risk caused by the total duration of LMWH administration (result not shown) disappeared: (OR 0.94, 95% CI 0.86 to 1.03). After exclusion of the aforementioned 18 cases, dental procedures (OR 3.32, 95% CI 1.22 to 9.04) and creatinine clearance ≤40 versus >60 ml/min (OR 5.03, 95% CI 1.25 to 20.26), p for linear trend=0.02 were identified as independent predictors of total bleeding in a model completed with the variables age, duration of periprocedural use of LMWH, and TE risk. The Hosmer-Lemeshov test resulted in a p-value of 0.47 and the model chi-square statistic yielded a significant result: p=0.01.

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

DISCUSSION

In our study we found that guideline adherence in bridging therapy in the region around Maastricht, the Netherlands is not optimal. The most striking finding is that 84.3% of all low TE risk patients were bridged with therapeutic doses of LMWH. Low TE risk does not warrant bridging therapy and certainly not with therapeutic doses of LMWH.[22] Furthermore, compared with other studies, we found high rates of total and major bleeding.[6,9,23,24] We were unable to find an association of this observed aggressive treatment with anticoagulants and the high bleeding rates, possibly due a lack of contrast in our population. Studies performed by Jaffer *et al.* and Robinson *et al.* identified postprocedural therapeutic doses of LMWH as a risk factor for bleeding.[6,11] In general, bridging therapy exposes the patient to additional risks, also including a risk of heparin-induced thrombocytopenia (HIT).[25] Interventions for which no bridging anticoagulation is indicated and VKA administration can simply be continued represented 27.9% of the total number of procedures performed in our cohort; a fairly high proportion. Possibly due to the fact that the majority of the participants were outpatients, the period of exposure to LMWH was much longer than necessary according to the ACCP guidelines; in outpatients rigidly performed INR testing is often not feasible.[26] Furthermore, due to a change in the anticoagulant regime in the outpatient setting the patient's compliance might be at risk; this might introduce an additional risk factor for bleeding or TE. Another possible explanation for prolonged LMWH administration might be the use of too low restart doses of VKA (i.e. the maintenance dose) instead of 1.5 to 2 times higher doses of acenocoumarol and phenprocoumon as advised in guidelines issued by the FNT.[27] Overall TE incidence was low and in concordance with some other studies;[6,9,23,24] no arterial TE occurred. We conclude that individual clinicians often do not act according to the current bridging guidelines; in the observed cohort the decision to administer therapeutic dosages of LMWH was not or barely influenced by surgical bleeding risk, TE risk, or renal insufficiency. Krahn *et al.* and Skolarus *et al.* report similar findings;[5,28] Gerson *et al.* on the other hand concluded that most people receiving bridging therapy were managed according to current society guidelines.[29] Possible explanations for non-adherence are the lack of familiarity with these guidelines, lack of awareness of the significance of consistent bridging practices, disagreement with the guidelines, and resistance to change.[30] It is also conceivable that physicians tend to over-treat patients because the threat of a TE is considered more severe than the threat of bleeding.[5]

Renal insufficiency appeared an independent predictor for total bleeding. Other studies support this finding;[1,14] the clearance of LMWH is primarily renal, the plasma half-life increases in patients with renal failure and dose reduction is advised in these patients following the Cockroft-Gault formula.[8,31] As far as we know only one study performed by Hammerstingl reported high TE risk as a risk factor for perioperative bleeding.[8] Possibly confounding biased this finding since in our analysis increasing TE risk was only found to be a risk factor for total bleeding in univariable analyses. An unexpected, novel finding is that dental

treatment inflicts a very high bleeding risk on patients. Most dental treatments do not warrant bridging therapy; instead, VKA continuation in combination with the oral administration of antifibrinolytic agents such as tranexamic acid is advised.[22] Several studies report that restarting LMWH in close proximity to the intervention might induce bleeding.[16,17] Our study does not support these findings; the observed high rate (28.8%) of missing values concerning this variable might have diluted this effect.

Strengths and limitations of study

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

CONCLUSIONS

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

Disclosure

The data were presented at ISTH congress, Amsterdam, the Netherlands on 1 July 2013: poster presentation.

REFERENCES

1. Cano O, Osca J, Sancho-Tello MJ, Olague J, Castro JE, Salvador A. Morbidity associated with three different antiplatelet regimens in patients undergoing implantation of cardiac rhythm management devices. Europace. 2011;13:395-401.
2. Tompkins C, Cheng A, Dalal D, et al. Dual antiplatelet therapy and heparin "bridging" significantly increase the risk of bleeding complications after pacemaker or implantable cardioverter-defibrillator device implantation. J Am Coll Cardiol. 2010;55:2376-82.
3. Li HK, Chen FC, Rea RF, et al. No increased bleeding events with continuation of oral anticoagulation therapy for patients undergoing cardiac device procedure. Pacing Clin Electrophysiol. 2011;34:868-74.
4. Ghanbari H, Feldman D, Schmidt M, et al. Cardiac resynchronisation therapy device implantation in patients with therapeutic international normalized ratios. Pacing Clin Electrophysiol. 2010;33:400-6.
5. Krahn AD, Healey JS, Simpson CS, Essebag V, Sivakumaran S, Birnie DH. Anticoagulation of patients on chronic warfarin undergoing arrhythmia device surgery: wide variability of perioperative bridging in Canada. Heart Rhythm. 2009;6:1276-9.
6. Jaffer AK, Brotman DJ, Bash LD, Mahmood SK, Lott B, White RH. Variations in perioperative warfarin management: outcomes and practice patterns at nine hospitals. Am J Med. 2010;123:141-50.
7. Ercan M, Bostanci EB, Ozer I, et al. Postoperative hemorrhagic complications after elective laparoscopic cholecystectomy in patients receiving long-term anticoagulant therapy. Langenbecks Arch Surg. 2010;395:247-53.
8. Hammerstingl C, Omran H. Perioperative bridging of chronic oral anticoagulation in patients undergoing pacemaker implantation--a study in 200 patients. Europace. 2011;13:1304-10.
9. Hammerstingl C, Omran H. Bridging of oral anticoagulation with low-molecular-weight heparin: experience in 373 patients with renal insufficiency undergoing invasive procedures. Thromb Haemost. 2009;101:1085-90.
10. Hammerstingl C, Schmitz A, Fimmers R, Omran H. Bridging of chronic oral anticoagulation with enoxaparin in patients with atrial fibrillation: results from the prospective BRAVE registry. Cardiovasc Ther. 2009;27:230-8.
11. Robinson M, Healey JS, Eikelboom J, et al. Postoperative low-molecular-weight heparin bridging is associated with an increase in wound hematoma following surgery for pacemakers and implantable defibrillators. Pacing Clin Electrophysiol. 2009;32:378-82.
12. Tolosana JM, Berne P, Mont L, et al. Preparation for pacemaker or implantable cardiac defibrillator implants in patients with high risk of thrombo-embolic events: oral anticoagulation or bridging with intravenous heparin? A prospective randomized trial. Eur Heart J. 2009;30:1880-4.
13. Tischenko A, Gula LJ, Yee R, Klein GJ, Skanes AC, Krahn AD. Implantation of cardiac rhythm devices without interruption of oral anticoagulation compared with perioperative bridging with low-molecular weight heparin. Am Heart J. 2009;158:252-6.
14. Ahmed I, Gertner E, Nelson WB, House CM, Zhu DW. Chronic kidney disease is an independent predictor of pocket hematoma after pacemaker and defibrillator implantation. J Interv Card Electrophysiol. 2010;29:203-7.
15. Steger V, Bail DH, Graf D, Walker T, Rittig K, Ziemer G. A practical approach for bridging anticoagulation after mechanical heart valve replacement. J Heart Valve Dis. 2008;17:335-42.
16. Tafur AJ, McBane R, 2nd, Wysokinski WE, et al. Predictors of major bleeding in peri-procedural anticoagulation management. J Thromb Haemost. 2012;10:261-7.
17. Chow V, Ranasinghe I, Lau J, et al. Peri-procedural anticoagulation and the incidence of haematoma formation after permanent pacemaker implantation in the elderly. Heart Lung Circ. 2010;19:706-12.
18. Kiviniemi T, Karjalainen P, Pietila M, et al. Comparison of additional versus no additional heparin during therapeutic oral anticoagulation in patients undergoing percutaneous coronary intervention. Am J Cardiol. 2012;110:30-5.
19. Lahtela H, Rubboli A, Schlitt A, et al. Heparin bridging vs. uninterrupted oral anticoagulation in patients with Atrial Fibrillation undergoing Coronary Artery Stenting. Results from the AFCAS registry. Circ J. 2012;76:1363-8.
20. Eijgenraam P, Ten Cate H, Ten Cate-Hoek AJ. Safety and Efficacy of Bridging with Low Molecular Weight Heparins: A Systematic Review and Partial Meta-Analysis. Curr Pharm Des. 2013;19:4014-23.
21. Spyropoulos AC, Douketis JD, Gerotziafas G, Kaatz S, Ortel TL, Schulman S. Periprocedural antithrombotic and bridging therapy: recommendations for standardized reporting in patients with arterial indications for chronic oral anticoagulant therapy. J Thromb Haemost. 2012;10:692-4.
22. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:299S-339S.

23. Pengo V, Cucchini U, Denas G, et al. Standardized low-molecular-weight heparin bridging regimen in outpatients on oral anticoagulants undergoing invasive procedure or surgery: an inception cohort management study. Circulation. 2009;119:2920-7.

24. Malato A, Saccullo G, Lo Coco L, et al. Patients requiring interruption of long-term oral anticoagulant therapy: the use of fixed sub-therapeutic doses of low-molecular-weight heparin. J Thromb Haemost. 2010;8:107-13.

25. Jaffer AK, Brotman DJ, Chukwumerije N. When patients on warfarin need surgery. Cleve Clin J Med. 2003;70:973-84.

26. Deerhake JP, Merz JC, Cooper JV, Eagle KA, Fay WP. The duration of anticoagulation bridging therapy in clinical practice may significantly exceed that observed in clinical trials. J Thromb Thrombolysis. 2007;23:107-13.

27. van Dolder BD. De kunst van het doseren. Voorschoten: Federatie van Nederlandse trombosediensten; 2010.

28. Skolarus LE, Morgenstern LB, Froehlich JB, Lisabeth LD, Brown DL. Guideline-discordant periprocedural interruptions in warfarin therapy. Circ Cardiovasc Qual Outcomes. 2011;4:206-10.

29. Gerson LB, Michaels L, Ullah N, Gage B, Williams L. Adverse events associated with anticoagulation therapy in the periendoscopic period. Gastrointest Endosc. 2010;71:1211-7 e2.

30. Eisenstein DH. Anticoagulation management in the ambulatory surgical setting. AORN J. 2012;95:510-21 examination 22-4.

31. Harder S, Klinkhardt U, Alvarez JM. Avoidance of bleeding during surgery in patients receiving anticoagulant and/or antiplatelet therapy: pharmacokinetic and pharmacodynamic considerations. Clin Pharmacokinet. 2004;43:963-81.

32. Spyropoulos AC, Turpie AG. Perioperative bridging interruption with heparin for the patient receiving long-term anticoagulation. Curr Opin Pulm Med. 2005;11:373-9.