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Strategies and outcomes of periprocedural bridging therapy with low-molecular-weight heparin in patients with mechanical heart valves

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Abstract Patients with mechanical heart valves (MHV) undergoing invasive procedures often receive periprocedural bridging with low-molecular-weight heparin (LMWH). The bridging strategies used in real-life and the predictors for bleeding and thrombosis are not well studied. We retrospectively assessed patients with MHV that underwent invasive procedures requiring vitamin K antagonist interruption and LMWH bridging. Thromboembolic and bleeding events occurring up to 30 days after the procedures were recorded. Predictors of major bleeding events (MBEs) were analyzed with logistic regression. We evaluated 547 patients with MHV who underwent 275 procedures during a 6.5-year period. Bridging with LMWH was used in 185 procedures in a total of 117 patients. Combined pre- and post-operative bridging was the most frequently employed (63 %). Doses of LMWH were prophylactic in 96 (52 %) of the procedures and therapeutic in 89 (48 %). The procedure-related bleeding risk was evaluated as high in 70 (38 %) and low in 115 (62 %) of the procedures. There was a trend to more frequent use of prophylactic doses (61 %) in high-risk surgery, and more therapeutic doses (53 %) in low-risk ones. There were 36 bleeding episodes, 21 (11 % of procedures) of which were classified as MBEs, but there were no thromboembolic events. Most MBEs (n = 14; 67 %) occurred in surgeries with high bleeding risk. In the multivariate analysis, the bleeding risk of the surgery itself was the only independent predictor for MBEs. For patients with MHV receiving perioperative bridging with LMWH, the major predictor for MBE is the bleeding risk of the surgery.

Keywords Low-molecular-weight heparin · Mechanical heart valves · Bridging · Surgery · Bleeding

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Introduction

More than 4 million patients worldwide have undergone valve replacement surgery for valvular heart disease [1]. Patients with mechanical heart valves (MHV) are treated indefinitely with vitamin K antagonists (VKA), such as warfarin, due to an increased risk of thromboembolism. This risk is further augmented in patients with a history of stroke, atrial fibrillation, and previous thromboembolic events [2]. When patients with MHV subsequently undergo an invasive procedure, their oral anticoagulation treatment is in most cases temporarily withheld to avoid an increased risk of bleeding. As a result, these patients might be at an increased risk of valve thrombosis and cerebral or systemic embolism during this interruption, and require therefore "bridging" with a short-acting anticoagulant [3]. The most common options used are subcutaneous low-molecular-weight heparin (LMWH) and intravenous unfractionated heparin. LMWH is advantageous as it can be self-administered at home with a fixed, weight-based dose and is less costly and time-consuming [4–6]. Furthermore, intravenous unfractionated heparin is associated with a higher

frequency of thrombocytopenia [7]. Thus, LMWH is commonly used in periprocedural anticoagulation therapy as an alternative to VKA treatment [8, 9].

Few studies to date with large cohorts of MHV patients have assessed the use of LMWH for periprocedural bridging and the associated bleeding risk [3–5, 8–10]. Furthermore, it is unclear whether bridging should be used at all during invasive procedures, as its risks might outweigh its benefits [10, 11]. Currently, management of anticoagulation during invasive procedures varies widely as the evidence for recommendations in international guidelines are weak, requiring each patient to be evaluated individually [5, 12, 13].

We performed a retrospective study to review all patients in Stockholm City County with MHV and the perioperative bridging regimen used. In particular, we aimed to assess the outcomes of the periprocedural bridging regimens in terms of perioperative bleeding and thromboembolic events, as well as the associated risk factors.

Materials and methods

The study design was a retrospective assessment of all patients with MHV that underwent an invasive procedure requiring interruption of VKA treatment in combination with bridging therapy at 5 hospitals in the Stockholm area (Karolinska University Hospital in Solna and Huddinge, Danderyd Hospital, Södersjukhuset, and Södertälje Hospital), a catchment area of 2 million people, between January 1, 2007 and September 15, 2013. The local ethics board of Karolinska University Hospital approved the study and waived the requirement for informed consent. We included patients older than18 years with a MHV and undergoing an invasive procedure that required interruption of VKA, and receiving LMWH at any dose as bridging therapy before and/or after the procedure. For each patient, all medical records were searched for invasive procedures, and we recorded all thromboembolic and bleeding events within 30 days after the procedure. Patients excluded from the study were those who did not receive perioperative bridging at all and those who underwent emergent surgeries.

Three different LMWHs were used (dalteparin, enoxaparin, and tinzaparin) and at varying doses. We defined prophylactic dose as $\leq$100 IU/kg/day for dalteparin and tinzaparin, and $\leq$1 mg/kg/day for enoxaparin; therapeutic dose was defined as any dose higher than the upper limit of the prophylactic dose. The classification of bleeding risk associated with the procedure was adapted from Spyropoulos et al., modified so that hip and knee replacement surgeries were defined as high bleeding risk [14]. Moreover, experienced surgeons specialized in the respective fields were consulted for the classification of the procedural bleeding risk of surgeries not listed in the above study [14].

A thromboembolic event was defined as the occurrence of symptomatic, objectively verified arterial or venous thromboembolism, or cardiac valve thrombosis, as registered in the medical records of the patient. A major bleeding event was defined as recommended by the International Society on Thrombosis and Haemostasis [15]. The outcomes were adjudicated by two of the authors (A.Å. and A.M.), who were blinded to the bridging regimen used.

Statistical analysis

Continuous variables with skewed distribution are presented as medians and inter-quartile ranges (IQR). Univariate analysis was done with Chi square or Fisher's exact test for categorical data, and Mann–Whitney test for continuous variables with skewed distribution.

A logistic regression model was fitted for the dichotomous outcome of post-operative bleeding. The model was adjusted for age, sex, body weight, renal function (expressed as the creatinine clearance according to the Cockcroft–Gault formula), international normalized ratio (INR) on the day of intervention, the bleeding risk of the surgery, concomitant treatment with platelet inhibitors, and the bridging strategy used. Bridging with LMWH was divided into six categories depending on the timing of administration of LMWH (pre-operatively, post-operatively, or both) and the doses of LMWH used (prophylactic or therapeutic). A further sensitivity analysis was done with the total dose of LMWH administered or with the dose of LMWH expressed as IU/kg/day. Model fitness was assessed with the Hosmer–Lemeshow test. A p value <0.05 was considered to be statistically significant in a two-sided test. Statistical analyses were performed with the SAS® software version 9.4 (Cary, NC).

Results

Study population

We screened the medical records of 547 patients with MHVs, of whom 175 (32 %) underwent a total of 275 invasive procedures during the study period. Ninety (33 %) procedures were excluded from further analysis, as no perioperative bridging was given (emergency surgery in 74, and planned surgery with VKA discontinuation alone in 16 patients). The remaining 185 procedures in 117 patients constituted the basis for our study.

The baseline characteristics of the study population are presented in Table 1. The median age of the cohort was 62

Table 1 Basic characteristics of the study population according to major bleeding events

Covariate	Patients with major bleeding events		*p* value[a]
	No (n = 104)	Yes (n = 13)	
Age, median (IQR)	60 (16.0)	66 (13.0)	0.15
Sex, male [n (%)]	62 (59.6)	10 (76.9)	0.37
Weight, median (IQR)	76 (20.0)	75 (25.0)	0.69
eGFR [mL/min (%)]			0.94
≥80	63 (60.6)	8 (61.5)	
50–80	30 (28.9)	5 (38.5)	
30–50	6 (5.8)	0	
<30	5 (4.8)	0	
MHV [n (%)]			0.04
Aortic	80 (76.9)	6 (46.2)	
Aortic + Mitral	7 (6.7)	3 (23.1)	
Mitral	14 (13.5)	3 (23.1)	
Tricuspid	3 (2.9)	1 (7.7)	
Co-morbidities [n (%)]			
Diabetes	17 (16.4)	2 (15.4)	1.00
Hypertension	49 (47.1)	5 (38.5)	0.77
Heart failure	31 (29.8)	5 (38.5)	0.54
Previous stroke	16 (15.4)	0 (0.0)	0.21
Concomitant medication [n (%)]			
Antiplatelet agents	7 (6.7)	1 (7.7)	1.00
NSAID	5 (4.8)	0 (0.0)	1.00
INR pre-op, median (IQR)	1.4 (1.3–1.6)	1.6 (1.3–1.7)	0.27

eGFR Estimated glomerular filtration rate, *MHV* mechanical heart valve, *NSAID* non-steroidal anti-inflammatory drug, *INR* international normalized ratio, *IQR* inter-quartile range

[a] Calculated with Chi square or Fisher's exact test for categorical data, and Mann–Whitney for continuous variables with skewed distribution

(IQR 52–86) years and most of the patients were men (n = 72, 62 %). The majority of the patients had MHV in the aortic position (n = 86, 74 %), followed by the mitral (n = 17, 15 %), and both the aortic and mitral positions (n = 10, 9 %). The remaining 4 (3 %) had tricuspid mechanical valves. Atrial fibrillation was present in 39 (33 %), and previous stroke in 16 (14 %) patients. Eight (7 %) had concomitant treatment with an antiplatelet agent at the time of surgery.

Invasive procedures and bridging

VKA treatment was discontinued at a median (IQR) of 3 (2–4) days before surgery, resulting in a median (IQR) INR on the day of surgery of 1.4 (1.3–1.6). Combined pre- and post-operative bridging with LMWH was the most frequently utilized strategy (63 %), followed by post-operative bridging only (35 %), and then bridging before surgery only in 2 %. In a slightly larger proportion of surgeries, prophylactic rather than therapeutic doses of LMWH (52 vs. 48 %, respectively) were used for bridging. The details of the bridging strategies used perioperatively according to the type of surgery are listed in Table 2.

Patients with mechanical mitral valves were more frequently bridged with therapeutic doses of LMWH (55 %), and they received more frequently bridging pre-operatively (70 %) as compared to those with mechanical aortic valves (44 and 62 %, respectively). These differences were, however, not statistically significant (*p* value 0.33 and 0.32, respectively). The utilization of the different bridging strategies according to the type of MHV, listed from the strategies presumed to be associated with the lowest to highest bleeding risk, is presented in Table 3.

Endoscopy was the most common type of intervention requiring bridging (21 %), followed by vascular surgery and minor surgeries (20 and 18 %, respectively). Depending on the type of surgery, the risk of perioperative bleeding was judged to be high in 70 (38 %) and low in 115 (62 %). There was a trend toward a more frequent utilization of prophylactic LMWH doses in high bleeding

Table 2 Bridging strategies for the different surgery categories

Surgery	Prophylactic LMWH doses			Therapeutic LMWH doses			Total
	Bridging pre-op	Bridging post-op	Bridging pre- and post-op	Bridging pre-op	Bridging post-op	Bridging pre- and post-op	
Biopsy	0	2	3	0	1	2	8
Mastectomy	0	0	2	0	1	0	3
CNS surgery	0	0	0	0	0	1	1
ENT surgery	0	3	0	0	1	0	4
Endoscopy	0	2	8	1	3	25	39
Endovascular surgery	0	1	0	0	1	3	5
Laparotomy	0	0	1	0	0	0	1
Major urological	0	1	0	0	0	1	2
TURP	0	0	3	0	0	1	4
Major gynecological	0	0	4	0	0	1	5
Minor gynecological	0	1	3	0	0	1	5
Major orthopedic	0	1	8	0	0	2	11
Minor orthopedic	0	3	3	1	3	2	12
Minor surgery	1	9	8	0	7	9	34
Minor abdominal	0	2	3	0	0	2	7
Pacemaker implantation	0	1	1	0	0	0	2
Paracentesis	0	1	1	0	0	3	5
Vascular	1	12	8	0	8	8	37
Total	2	39	56	2	25	61	185

LMWH Low-molecular-weight heparin, *CNS* central nervous system, *ENT* ear, nose and throat, *TURP* trans-urethral resection of the prostate

Table 3 Bridging strategy according to the type of mechanical heart valve

Bridging	Aortic + Mitral	Mitral	Aortic	Tricuspid	Total
Pre-op, prophylactic doses [n (%)]	0 (0)	0 (0)	1 (1)	1 (14)	2 (1)
Post-op, prophylactic doses [n (%)]	2 (10)	8 (24)	28 (23)	1 (14)	39(21)
Pre-op, Therapeutic doses [n (%)]	1 (5)	1 (3)	0 (0)	0 (0)	2 (1)
Pre- and post-op, prophylactic doses [n (%)]	9 (43)	7 (21)	40 (32)	0 (0)	56 (30)
Post-op, therapeutic doses [n (%)]	3 (14)	2 (6)	19 (15)	1 (14)	25 (14)
Pre- and post-op, therapeutic doses [n (%)]	6 (29)	15 (45)	36 (29)	4 (57)	61 (33)
Total	21	33	124	7	185

risk surgery (n = 43, 61 %), and therapeutic doses in low risk ones (n = 61, 53 %) ($p = 0.06$). Bridging was started pre-operatively in a significantly higher proportion of procedures with low bleeding risk as compared to high risk ones (67 vs. 51 %, $p = 0.026$).

Bleeding

There were a total of 36 bleeding events in 22 patients who received bridging therapy with LMWH, and 21 events (in 11 % of all procedures) were judged as MBEs. Two-thirds of all MBEs (n = 14; 67 %) occurred in surgery classified as having high bleeding risk. About one-third of all MBEs (n = 8, 38 %) occurred in conjunction with major vascular surgery. The assessed bleeding risk of the invasive procedures/surgeries was the only significant predictor of major bleeding (14 of 70 high-risk procedures = 20 % vs. 7 of 108 low-risk procedures = 6.5 %) in univariate analysis (logrank $p = 0.009$) (Fig. 1).

Most MBEs occurred in patients receiving pre- and post-operative bridging (62 %), followed by those receiving post-operative bridging only (33 %), while 5 % of all MBEs occurred in patients that received pre-operative bridging only ($p = 0.59$). There was a trend to higher rate of MBEs in patients receiving prophylactic doses of LMWH (71 %) compared to those on therapeutic doses (29 %, $p = 0.06$).

In the multivariate analysis with logistic regression, the bleeding risk of the surgery was the only significant

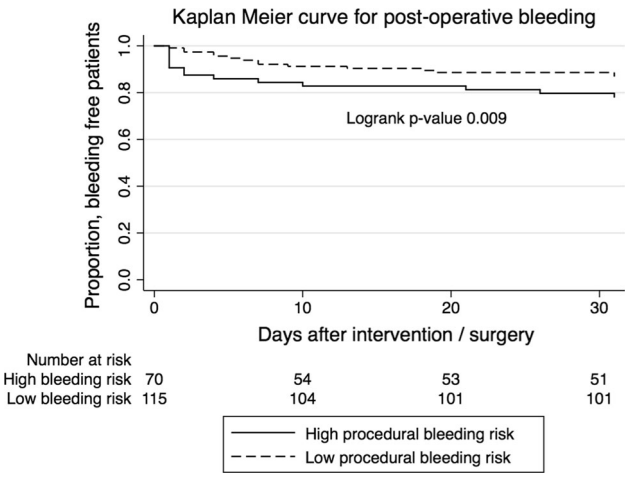

Fig. 1 Survival without major bleeding according to bleeding risk of procedure

predictor of the development of MBE during perioperative bridging with LMWH [odds ratio (OR) for MBE in high versus low bleeding risk surgery = 4.5; 95 % confidence interval (CI) 1.5–13.4]. The dose (therapeutic or prophylactic) and the timing of administration (before, before and after, or only after surgery) of LMWH were not significant predictors of MBE in the model. Other variables in the regression model, including age, sex, weight, renal function, pre-operative INR, concomitant treatment with antiplatelet agents or non-steroidal anti-inflammatory agents, or renal function were not significantly associated with the development of MBE. In a further sensitivity analysis, the dose of LMWH, expressed as total units or as units per kilogram body weight, was not associated with the risk of perioperative MBE (data not shown).

Since the recommended INR for patients requiring VKA interruption for major procedures is <1.5 [14], the analysis was adjusted to include only patients whose INR was <1.5 pre-operatively. Even when the analysis was limited to patients with a pre-operative INR < 1.5 (n = 99, 8 MBE in total), the results of the adjusted analysis did not change, with procedural bleeding risk being the only significant predictor of major bleeding (OR 12.0, 95 % CI 1.4–108.8, *p* value 0.02).

During the study period, a recommended standard protocol for bridging with LMWH existed at Karolinska University Hospital. Altogether only 12 patients were managed according to this protocol. No further statistical analysis was done on this population due to its small size.

Thromboembolic events

There were no cardiac valvular, arterial, or venous thromboembolic events registered during 30 days after the invasive procedure/surgery in any of the patients.

Discussion

This retrospective real-life study investigated patients with MHV, admitted to five different hospitals in the Stockholm area. One hundred and seventeen of these patients underwent 185 invasive procedures with warfarin interruption and bridging with LMWH. There were 21 MBEs (11 % of procedures) in this population, but no thromboembolic complications. The major predictor for MBE was the bleeding risk of the surgery. The dose and timing of LMWH administration were not significantly associated with the development of MBE. We had rather similar numbers of patients bridged with prophylactic versus therapeutic doses of LMWH. Despite prophylactic doses trending to be more frequently used in high bleeding risk surgery than in low bleeding risk procedures, the number of bleeding complications were higher in the former group. This was confirmed by the adjusted analysis, and our interpretation is therefore that the dose of LMWH plays only a minor role, if any, in this clinical setting. Furthermore, even if patients with major bleeding had a higher (though non-significant) INR preoperatively, this INR did not have a significant impact on the risk of post-operative bleeding in the adjusted analysis. The pre-operative median INR values listed in Table 1 are those on the day of intervention. At this point in time, VKA had already been interrupted, and LMWH bridging had most likely already been initiated in these patients.

While many studies [3, 8, 16] have found periprocedural bridging with LMWH to be an effective means of preventing thromboembolic events in patients with MHV, several studies report significant bleeding events associated with LMWH bridging [10, 12, 13]. Therefore, the benefit of thromboembolism prevention must be weighed against the increased risk of bleeding, and each patient needs to be evaluated individually before selecting the best periprocedural anticoagulation regimen. A large randomized clinical trial (BRIDGE, ClinicalTrials.gov NCT00786474) is in fact currently evaluating whether bridging anticoagulation in patients with atrial fibrillation causes more bleeding than protects against cardioembolism. Some studies also suggest that the incidence of hemorrhage increases with extended duration of LMWH treatment, and that post-procedural heparin use should be reserved for patients with the highest thromboembolic risk (patients with mitral MHV, multiple MHVs, prior stroke or atrial fibrillation) [4, 16]. In contrast, our results propose that the risk of bleeding is more dependent on the type of procedure performed, rather than on the regimen of LMWH bridging. A study by Beyer-Westendorf et al. that investigated periprocedural bridging with discontinuation of novel oral anticoagulants supported this finding [17].

There are several aspects of the study that support the validity of the results obtained. First, this investigation was a real-life study with a patient registry that included consecutive patients in a defined geographical area. This creates a more representative sample, reduces the risk of selection bias, and increases the external validity of the results. Second, the medical records of all patients were scrutinized for LMWH regimen, INR and hemoglobin level, type of invasive procedures, bleeding complications, transfusion therapy, and thromboembolic events, which enhances the reliability of the results obtained compared to a registry study only. Third, the invasive procedures included in this study varied greatly in their nature, resulting in inclusion of most of the common surgical procedures. This increases the generalizability of our results and further strengthens the external validity of the study.

Several limitations of this study also need to be acknowledged. First of all, the retrospective design of the study may increase the risk of selection bias and an unbalanced exposure of the various groups to different risk factors. However, due to the inclusion of all patients from the Stockholm area and the absence of any loss-to-follow-up in our data, the risk of selection bias is diminished. Furthermore, the use of adjusted analysis with regression analysis minimises the impact of imbalance of risk factors in the various groups. While we were able to include consecutive patients in Stockholm in our registry, we recognize that there might have been patients that underwent invasive procedures outside of Stockholm and were thus unknown to us. This would mainly apply to emergency procedures, which we anyhow excluded from our analysis. Furthermore, patients may not have reported a minor bleeding or thromboembolic event that occurred after the discharge from the hospital, or they may have presented to a hospital outside of our registry if they were visiting another city at the time. As a result, our findings may underestimate the risk of bleeding and thromboembolic events. As well, our study did not evaluate a standard protocol with weight-based doses of LMWH for bridging therapy. Even though such a protocol existed, it was not widely distributed or used. The responsible physician or surgeon therefore managed each patient individually. Our study did not include a control group, and therefore we cannot compare our periprocedural bridging regimen with other methods that do not employ bridging. Additional studies, such as randomized clinical trials that compare one bridging strategy with regimens that utilize alternative doses of LMWH, other anticoagulants, or no periprocedural bridging, are thus needed to identify the optimal management. Another limitation of the study is the large number of surgical procedures that were included, making it impossible to draw conclusions about any single one of those. Finally, the number of patients is limited and we may therefore have failed to identify some risk factors for major bleeding.

We conclude that for patients with MHV on long-term VKA receiving perioperative bridging with LMWH, the major predictor for MBE is the bleeding risk of the surgery itself. Other variables, including age, sex, weight, renal function, pre-operative INR, concomitant treatment with antiplatelet agents or NSAIDs, and dose and timing of LMWH administration are not significantly associated with the development of MBE in the population we analyzed. Additional studies are needed to strengthen these results and further investigate perioperative anticoagulation management in patients with MHV.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Sun JC, Davidson MJ, Lamy A, Eikelboom JW (2009) Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. Lancet 374(9689):565–576. doi:10.1016/S0140-6736(09)60780-7
2. Kulik A, Rubens FD, Wells PS, Kearon C, Mesana TG, van Berkom J, Lam BK (2006) Early postoperative anticoagulation after mechanical valve replacement: a systematic review. Ann Thorac Surg 81(2):770–781. doi:10.1016/j.athoracsur.2005.07.023
3. Hammerstingl C, Tripp C, Schmidt H, von der Recke G, Omran H (2007) Periprocedural bridging therapy with low-molecular-weight heparin in chronically anticoagulated patients with prosthetic mechanical heart valves: experience in 116 patients from the prospective BRAVE registry. J Heart Valve Dis 16(3): 285–292
4. Dattilo G, Tulino D, Lamari A, Tulino V, Marte F, Patane S (2011) Treatment failure of low molecular weight heparin in a patient with an aortic mechanical prosthesis. Int J Cardiol 146(2): e30–32. doi:10.1016/j.ijcard.2008.12.180
5. Fanikos J, Tsilimingras K, Kucher N, Rosen AB, Hieblinger MD, Goldhaber SZ (2004) Comparison of efficacy, safety, and cost of low-molecular-weight heparin with continuous-infusion unfractionated heparin for initiation of anticoagulation after mechanical prosthetic valve implantation. Am J Cardiol 93(2):247–250
6. Spyropoulos AC, Frost FJ, Hurley JS, Roberts M (2004) Costs and clinical outcomes associated with low-molecular-weight heparin vs unfractionated heparin for perioperative bridging in patients receiving long-term oral anticoagulant therapy. Chest 125(5):1642–1650
7. Junqueira DR, Perini E, Penholati RR, Carvalho MG (2012) Unfractionated heparin versus low molecular weight heparin for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. doi:10.1002/14651858.CD007557.pub2
8. Spyropoulos AC, Turpie AG, Dunn AS, Kaatz S, Douketis J, Jacobson A, Petersen H, Investigators R (2008) Perioperative bridging therapy with unfractionated heparin or low-molecular-weight heparin in patients with mechanical prosthetic heart valves on long-term oral anticoagulants (from the REGIMEN registry). Am J Cardiol 102(7):883–889. doi:10.1016/j.amjcard.2008.05.042

9. Bucci C, Geerts WH, Sinclair A, Fremes SE (2011) Comparison of the effectiveness and safety of low-molecular weight heparin versus unfractionated heparin anticoagulation after heart valve surgery. Am J Cardiol 107(4):591–594. doi:10.1016/j.amjcard.2010.10.020
10. Douketis JD, Johnson JA, Turpie AG (2004) Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. Arch Intern Med 164(12):1319–1326. doi:10.1001/archinte.164.12.1319
11. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R, American College of Chest Physicians (2012) Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 141(2 Suppl):e326S–350S. doi:10.1378/chest.11-2298
12. Bui HT, Krisnaswami A, Le CU, Chan J, Shenoy BN (2009) Comparison of safety of subcutaneous enoxaparin as outpatient anticoagulation bridging therapy in patients with a mechanical heart valve versus patients with nonvalvular atrial fibrillation. Am J Cardiol 104(10):1429–1433. doi:10.1016/j.amjcard.2009.06.065
13. Jaffer AK, Brotman DJ, Bash LD, Mahmood SK, Lott B, White RH (2010) Variations in perioperative warfarin management: outcomes and practice patterns at nine hospitals. Am J Med 123(2):141–150. doi:10.1016/j.amjmed.2009.09.017
14. Spyropoulos AC, Douketis JD (2012) How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood 120(15):2954–2962. doi:10.1182/blood-2012-06-415943
15. Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis (2010) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 8(1):202–204. doi:10.1111/j.1538-7836.2009.03678.x
16. Daniels PR, McBane RD, Litin SC, Ward SA, Hodge DO, Dowling NF, Heit JA (2009) Peri-procedural anticoagulation management of mechanical prosthetic heart valve patients. Thromb Res 124(3):300–305. doi:10.1016/j.thromres.2009.01.011
17. Beyer-Westendorf J, Gelbricht V, Forster K, Ebertz F, Kohler C, Werth S, Kuhlisch E, Stange T, Thieme C, Daschkow K, Weiss N (2014) Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J 35(28):1888–1896. doi:10.1093/eurheartj/eht557