

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

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Background and aim of the study: The study aim was to determine the safety and feasibility of a standardized bridging regimen in patients with mechanical heart valves at high thromboembolic risk, using low-molecular-weight heparin (LMWH).

Methods: Since the year 2000, all patients at the authors' institution, with mechanical heart valves and a need for periprocedural interruption of oral anticoagulation (OAC), were prospectively enrolled in this registry. Patients were treated with enoxaparin following a pre-specified, standardized bridging regimen. The main outcome measures were the incidence of hemorrhagic or thromboembolic events. The follow up period was 30 days after hospital discharge.

Results: A total of 116 patients was included (31 with mitral valve replacement, 76 aortic valve replacement, nine double valve replacement). Patients underwent either major surgery (n = 25), minor surgery (n = 36), pacemaker implantation (n = 21), or coronary catheterization (n = 34). Bridging therapy with enoxaparin was administered for a mean of 7.0

± 4.6 days. Eighteen patients (15.5%) were treated as outpatients. In 35 patients (34%) with renal impairment (creatinine clearance <50 ml/min), LMWH dosage was halved. No thromboembolic (95% CI 0-3.1%) and only one major bleeding complication occurred (0.86%; 95% CI 0.02-4.7%); minor bleeding occurred in 10 patients (8.6%; 95% CI 4.2-15.3%). The hemorrhages arose after a mean of 5.4 ± 1.4 days LMWH therapy.

Conclusion: Bridging therapy following a standardized LMWH-based regimen with enoxaparin was effective and relatively safe in a large cohort of patients with mechanical heart valves. Extended duration of LMWH therapy seems to promote the incidence of hemorrhage. Neither dose reduction in patients with renal impairment nor outpatient treatment affected the safety and efficacy of this bridging regimen. These findings warrant that more extensive studies be conducted to investigate the safety of this approach.

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Thromboembolism may be a life-threatening complication in patients with prosthetic mechanical heart valves. In these patients, lifelong, effective antithrombotic therapy is indicated to reduce the risk of thromboembolism. Oral vitamin K antagonists are prescribed universally, their dose being guided by achieving a target International Normalized Ratio (INR), according to current guidelines, with a range of 2.0 to 3.5 for most mechanical heart valves (1). In patients requiring temporary interruption of oral anticoagulation (OAC) during surgery or invasive procedures, a bridging strategy with either unfractionated

heparin (UFH) or low-molecular-weight heparin (LMWH) is recommended to prevent thromboembolic complications (2-4). Traditionally, most cardiologists have used UFH as a short-term anticoagulant when bridging patients after mechanical heart valve replacement, although the safety and efficacy of this approach has not been validated by large randomized trials or cohort studies (5-9). More recently, physicians have tended to select LMWH in non-pregnant patients due to the more predictable and rapidly reached anticoagulant effect (10-12). Due to its high bioavailability, LMWH can be administered subcutaneously (sc) on a body-weight basis, and self-administration of anticoagulant therapy as an outpatient provides the possibility of significant cost savings compared with continuous intravenous UFH infusion in hospital. Particularly in postoperative mechanical heart valve replacement patients, there seems to be a reluctance

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among physicians to follow the high-dose requirements for the initial bolus and subsequent infusion therapy with UFH, for fear of precipitating bleeding complications (13). According to recently published datasets and clinical trials, bridging therapy with enoxaparin at a therapeutic dose of 1 mg/kg (sc) every 12 h seems to be associated with a low rate of thromboembolism and, compared to UFH, is a safe and effective approach for the periprocedural management of patients with prosthetic valves (14). However, few studies have been conducted to validate the safety and efficacy of either UFH or LMWH in this setting, and consensus has yet to be established on the optimum treatment protocol. Current guidance from the American College of Chest Physicians recommends that, for patients at a high risk of thromboembolism, OAC therapy should be withdrawn approximately four days before surgery to allow the INR to return to near-normal values, and patients should be treated with therapeutic-dose UFH or LMWH as the INR falls below therapeutic range. Following surgery, OAC therapy should be reinstated under concomitant therapy with UFH or LMWH until the INR is 2.0 to 3.0 (2). However, these were only grade 2C recommendations, based on experts' opinions, due to relatively weak evidence being available at the time of publication. Furthermore, there is a lack of evidence as to how bridging therapy should be conducted in patients with renal impairment; in most published clinical trials, elderly patients and those with a creatinine clearance (CrCl) <50 ml/min were excluded. Due to the renal excretion of LMWH, patients with renal insufficiency are at risk for accumulation of anticoagulant, followed by increasing antithrombotic effects and a cumulative tendency towards hemorrhage. Therefore, current guidelines propose a dose reduction of LMWH in case of severe renal impairment. However, this therapeutic approach has not been validated in either clinical trials or prospective registries.

The aim of the ongoing BRAVE registry (Bonn Registry for Alternative periprocedural Anticoagulation to Prevent Vascular Events) is to document, prospectively, the safety, efficacy and feasibility of a standardized LMWH bridging regimen in patients under OAC who require surgery or an invasive procedure with a need for an interruption of OAC therapy. Herein is reported the safety, efficacy and feasibility of bridging high-risk, non-pregnant patients with mechanical heart valves.

Clinical material and methods

Patients

At the present authors' institution, all patients with mechanical heart valves, who were scheduled to

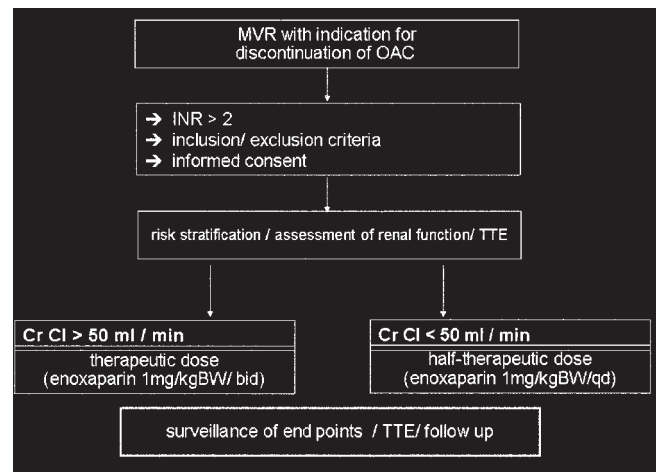


Figure 1: Study flow chart. Cr Cl: Creatinine clearance; INR: International Normalized Ratio; MVR: Mechanical valve replacement; TTE: Transthoracic echocardiography.

undergo elective surgery or invasive procedures with indication for alternative periprocedural anticoagulant therapy during interruption of OAC, were prospectively enrolled into the registry. Patients underwent a complete clinical evaluation at the time of enrolment, and also at the end of the study. Echocardiography (Systems V® and Vivid 7; GE Medical Systems, Wisconsin, USA) was conducted at enrolment and at the end of the study in order to exclude cardiac thrombi and/or valvular thrombosis. The follow up period was 30 days after hospital discharge; clinical information was obtained by telephone call, if personal attendance was impossible.

Patients were excluded from the registry for the following reasons: discontinuation of OAC therapy more than one month before enrolment; body weight <45 kg; life expectancy <2 months; cerebral or gastrointestinal bleeding within the previous six months; known allergy to UFH or LMWH; previous heparin-induced thrombocytopenia (HIT); acute neurological deficits or embolism; chronic liver disease; severe renal insufficiency; thrombocytopenia; endocarditis; pregnancy; and known fibrinolytic disorders (see Fig. 1). Minor surgery was defined as a surgical procedure without the use of general anesthesia or respiratory assistance. Major surgery was classified as any surgical procedure that involved the use of general anesthesia, with the need for respiratory assistance.

Periprocedural anticoagulation

Following the results of the prospective randomized EASE study (12), enoxaparin was chosen as the bridging anticoagulant. All patients were treated following a pre-specified bridging strategy (Fig. 2a and b). At four to six days before the procedure, treatment with phenprocoumon was interrupted, while the INR was

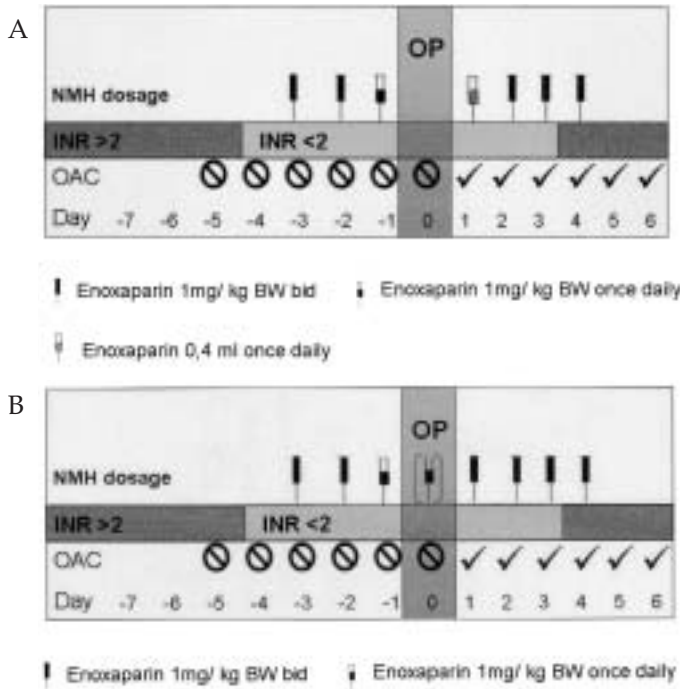


Figure 2: Treatment regimen for periprocedural anticoagulation in patients with mechanical heart valve replacement according to interventional bleeding risk. a) Bridging scheme before and after intervention with high bleeding risk including pacemaker implantation. b) Bridging scheme for interventions with non-high bleeding risk. According to interventional bleeding risk, effective anticoagulant therapy was withheld post-procedurally and LMWH administered in prophylactic dosage to avoid deep vein thrombosis if indicated.

monitored daily for 48 h after interruption of OAC and patients were administered subcutaneous enoxaparin (1 mg/kg) twice daily when the INR fell below 2.0. INR was determined daily, after the reintroduction of OAC when INR was near effective in order to avoid over-anticoagulation with an increased risk of hemorrhage. Procedures were performed at an INR of <1.5. Enoxaparin therapy was withheld on the evening before the procedure, and restarted at 12-48 h post-procedurally, according to the intervention's hemorrhagic risk. In patients who underwent pacemaker implantation, therapeutic anticoagulant therapy was restarted at least 24 h after the procedure. In patients with renal failure (defined as estimated CrCl 20-50 ml/min, according to the Cockcroft-Gault formula), the enoxaparin dose was reduced by 50%. Phenprocoumon was restarted post-procedurally under concomitant LMWH therapy until an effective INR was reinstated. During interruption of high-dose LMWH therapy, enoxaparin was administered following the low-dose requirements for thrombosis prophylaxis.

Outpatient treatment was defined as a discontinua-

tion of OAC therapy and commencement of LMWH therapy before hospital admission, followed by post-operative initiation of OAC therapy under concomitant LMWH therapy and hospital discharge before re-achievement of therapeutic INR. In these patients, echocardiography was performed at the start of bridging therapy and after the reintroduction of OAC.

Endpoints

The primary efficacy endpoint was incidence of thromboembolic complications, defined as clinical signs of stroke, transient ischemic attack, arterial embolism or myocardial infarction due to coronary embolism. The primary safety endpoint was the incidence of major bleeding complications. Secondary endpoints were minor bleeding, valvular thrombosis detected by echocardiography, HIT, thrombocytopenia due to other causes, and any other adverse events. Major bleeding was defined as bleeding requiring acute treatment/reoperation, medical evaluation, or transfusion with at least 2 units of blood; intracranial hemorrhage or retroperitoneal hemorrhage; a need for prolonged hospitalization; and all fatal and life-threatening bleeding. Minor bleeding was defined as all other types of bleeding, including hematoma of >5 cm at the LMWH injection site or prolonged bleeding at the section site. Follow up was 30 days by telephone call.

Statistical analysis

Results are shown in natural units. Categorical variables were reported as frequencies and relative frequencies (percentages). For continuous variables, number of patients, mean \pm SD were provided. In case of comparisons *between* groups, two-tailed *t*-tests were used, while in case of comparisons *within* groups, two-tailed paired *t*-tests were used. For the event rates, 95% confidence intervals (CI) were provided using the method of Clopper-Pearson. Data were prospectively collected and analyzed using StatView software (version 5.0, SAS Institute, Cary, NC, USA). In addition, StatXact (version 6, Cytel Studio, Cambridge, MA, USA) was used to calculate exact *p*-values for categorical data.

Results

Among 116 patients with mechanical heart valves who were treated with enoxaparin, 76 had mechanical aortic valve replacement (AVR), 31 mitral valve replacement (MVR), and nine double valve replacement (DVR) (Table I). Patients tended to be elderly (mean age 71.1 ± 11.1 years), with a high coincidence of cardiovascular and major thromboembolic risk factors (4) (arterial hypertension, 61%; diabetes mellitus, 20%;

Table I: Valve type, baseline characteristics and surgical interventions.

Parameter	No. of patients
Valve type	
Aortic valve replacement	76 (65.5)
Mitral valve replacement	31 (26.7)
Aortic + mitral valve replacement	9 (7.8)
Baseline characteristics	
Male gender	65 (56)
Age (years)*	71.1 ± 11.1
Arterial hypertension	70 (61)
Diabetes mellitus	23 (20)
Thromboembolism	19 (16.4)
Congestive heart failure	51 (44)
Cr Cl (ml/min)*	98.5 ± 39.7
Major surgery	25 (22)
Minor surgery (endoscopy)	36 (31)
Pacemaker implantation	21 (18)
Coronary catheterization	34 (29)
OAC duration (days)*	7.0 ± 4.6
Outpatient treatment	18 (15.5)

*Mean ± SD.

Values in parentheses are percentages.

Cr Cl: Creatinine clearance; OAC: Oral anticoagulation.

prior thromboembolism, 16%; congestive heart failure (CHF), 44%; atrial fibrillation (AF), 41%) (Table I). Patients with MVR and/or DVR had more often a history of embolism, a higher prevalence of heart failure, and presented more frequently with AF as compared to patients with AVR. All patients with mechanical heart valves in the mitral position, or after DVR, were considered at very high thromboembolic risk.

The types of valve implanted and the prevalence of concomitant thromboembolic and cardiovascular risk factors are listed in Table II. Among the 76 AVR patients, only three had no additional major thromboembolic risk factor (defined as history of thromboembolism, concomitant AF, left atrial dilatation, or CHF). Of note, these three patients were aged over 75 years (mean age 78.7 ± 3.7 years) and, according to current recommendations on anticoagulant therapy in patients after mechanical valve replacement (2,4), they were categorized at high thromboembolic risk with need for alternative anticoagulant therapy after interruption of OAC. Furthermore, six of the AVR patients had one or two additional major risk factors, while the other 67 (88%) had three or more major thromboembolic risk factors with a high coincidence of AF and/or CHF; this included 21 patients with older valve types (Starr-Edwards, Björk-Shiley and Medtronic Hall). Hence, all AVR patients were considered to be at relevant thromboembolic risk, and most were at very high thromboembolic risk according to their age and/or concomitant major risk factors (Table II). Overall 25 patients underwent major surgery, 36 minor surgery, 21 had pacemakers implanted, and 34 underwent coronary catheterization (including 14 percutaneous coronary interventions).

Table II: Concomitant risk factors and types of valve implanted.

Risk factor/ valve type	AVR (n = 76)	MVR (n = 31)	DVR (n = 9)
Risk factor			
History of TE	11 (15)	6 (21)	2 (25)
CHF	32 (42)	15 (48)	4 (44)
AF	22 (29)	20 (65)	6 (67)
LA dilatation	34 (45)	20 (65)	7 (78)
Valve type			
St. Jude Medical	31 (41)	15 (48)	5 (55)
Omnicarbon	23 (30)	7 (22)	2 (22)
ATS	1 (1.5)	0 (0)	0 (0)
Björk-Shiley	12 (16)	3 (9.6)	1 (11)
Starr-Edwards	2 (2.6)	0 (0)	0 (0)
Medtronic Hall	7 (9.2)	1 (3.2)	1 (11)
Unknown	2	5	2

Values in parentheses are percentages.

AF: Atrial fibrillation; AVR: Aortic valve replacement; CHF: Congestive heart failure; DVR: Double valve replacement; LA: Left atrial; MVR: Mitral valve replacement; TE: Thromboembolism.

Table III: Types of intervention and classification according to bleeding risk.

Intervention	No. of patients
High bleeding risk (n = 31)	
Abdominal surgery	6 (19)
Thoracic surgery	9 (29)
Neurosurgery	2 (6.5)
CABG	4 (13)
Other cardiovascular surgery	4 (13)
Interventional endoscopy	6 (19)
Non-high bleeding risk (n = 64)	
Dermatological surgery	4 (6.3)
Thoracic drainage	2 (3.1)
Dental surgery	4 (6.3)
Cataract surgery	2 (3.1)
Endoscopy	18 (28)
Cardiac catheterization	34 (56)
Pacemaker	21

Values in parentheses are percentages.
CABG: Coronary artery bypass grafting.

The types of intervention conducted in the study population, and classification according to hemorrhagic risk, are listed in Table III. Renal insufficiency with a CrCl <50 ml/min was present in 35 patients (34%), with a range of 20 to 50 ml/min. Of the latter patients, eight (6.9%) had a CrCl of 20-30 ml/min.

Transthoracic echocardiography performed at the beginning and end of bridging therapy showed no relevant increase in the transvalvular mean pressure gradients and/or peak velocities; no patient presented with echocardiographic signs of mechanical valve thrombosis (Table IV).

Patients received bridging therapy with enoxaparin for a mean of 7.0 ± 4.6 days, when the INR was ineffective. Eighteen patients (15.5%) were treated as outpatients.

Among the 116 patients evaluated, there were no thromboembolic complications (95% CI 0-3.1%), one major bleed (95% CI 0.02-4.7%) and 10 (8.6%) minor bleeds (95% CI 4.2-15.3%), including hematoma of >5 cm at the LMWH injection site or at the site of surgery. Of the latter patients with bleedings, three had a CrCl <50 ml/min. Four bleedings occurred after interventions assigned to high hemorrhagic risk, and seven after procedures at non-high bleeding risk (p = NS). The major hemorrhage was a spontaneous bleeding into the rectus muscle, five days after laparoscopic appendectomy, six days under LMWH therapy, and was not considered to be a procedure-related complication. All bleedings occurred after a pretreatment period with LMWH of about five to six days (mean 5.4 ± 1.4 days) (Table V). The total LMWH treatment time in patients with bleeds was not significantly different to that in patients without bleeding complications (7.0 ± 2.8 days versus 7.0 ± 4.5 days, p = NS).

Discussion

The results from the ongoing BRAVE registry show that a standardized periprocedural bridging therapy using a therapeutic dose of enoxaparin is effective and relatively safe in patients with mechanical heart valves, who are at a substantial high risk of thromboembolism. The duration of LMWH therapy seems to promote the incidence of hemorrhage. Outpatient treatment was feasible in 15.5% of patients, and did not affect the safety and efficacy of the bridging regimen. Moreover, this registry included a large percentage of patients with renal impairment in whom the enoxaparin dose was halved; this approach did not lead to an increase in thromboembolism in this subgroup.

Although, traditionally, most cardiologists have used UFH as anticoagulant when bridging patients after mechanical heart valve replacement (5), the safety and efficacy of this approach has not been validated by large, prospective randomized trials or cohort studies. Moreover, available data on bridging therapy with

Table IV: Echocardiographic findings before and after bridging therapy.

Parameter	Before bridging therapy	After bridging therapy	p-value
AVR			
P _{mean}	16.76 ± 7.31	16.5 ± 7.1	0.52 (NS)
V _{max}	1.9 ± 0.6	1.9 ± 0.6	0.34 (NS)
MVR			
P _{mean}	5.2 ± 3.7	5.0 ± 3.6	0.23 (NS)
V _{max}	1.3 ± 0.4	1.3 ± 0.3	0.36 (NS)

Values are mean ± SD.

AVR: Aortic valve replacement; MVR: Mitral valve replacement; P_{mean}: Mean pressure gradient; V_{max}: Peak velocity.

Table V: Details of bleeding complications during LMWH bridging therapy.

Adverse event	No. of events	Details	Bleed duration (days)*
Thromboembolism	0 (0) (CI 0-3.13)	-	-
Major bleeding	1 (0.86) (CI 0.02-4.7)	Day 5 after laparoscopic endoscopy	6
Minor bleedings	10 (8.6) (CI 4.2-15.3)	Hematoma >5 cm at injection site	5
	Hematoma >5 cm at injection site	6	
	Hematoma >5 cm at injection site	5	
	Hematoma >5 cm at injection site	7	
	Local hematoma after pacemaker implantation	5	
	Local hematoma after pacemaker implantation	6	
	Local hematoma after neurosurgery at day 7 under LMWH	7	
	Local minor bleed after dermatological surgery (treated with compression)	5	
	Local hematoma after coronary catheterization	2	
	Local hematoma after coronary catheterization	5	

Values in parentheses are percentages.

*While under LMWH therapy.

UFH in 91 non-pregnant patients, including 43 patients after mechanical heart valve replacement, showed a high incidence of bleeding complications (17.1%, with 5.5% major bleeds) (6-9). Most antithrombotic therapy-related complications in patients who have undergone mechanical heart valve replacement occur either intraoperatively or immediately following surgery, as a result of an interruption of OAC therapy due to hemorrhage (18). Therefore, lowering the perioperative bleeding incidence may be a key point of an effective and safe bridging regimen. Life-long OAC and short-term bridging therapy should provide effective protection against thromboembolic events, and a calculable low hemorrhagic risk.

The low incidence of major bleeding in the present patient cohort using a predefined bridging regime showed that a pre-specified therapeutic approach may enhance the safety of this therapy. Even if there were only a relatively small number of major surgical interventions, stopping OAC was indicated in all patients to avoid major hemorrhage. The total incidence of major and minor hemorrhage was very low compared to that cited by Spyropoulos et al. (20) and Kovacs et al. (18). Most bleeds manifested as a hematoma >5 cm, either at the injection site of the LMWH or at the site of surgery. These good results support the safety of this risk-adapted bridging regimen with a dose reduction of LMWH after interventions with high bleeding risk, and in patients with renal impairment.

The results of the present study provide more data to support the concept, that patients with mechanical valve replacement may be safely bridged with LMWH before and after procedures with an elevated bleeding risk (15-20).

In the present study, a high proportion of patients was included with MVR and DVR, together with patients with AVR and concomitant major thromboembolic risk factors (heart failure, AF and older valve types). These patients are at a particularly high risk of thromboembolism (1,4) and, therefore, must receive effective and reliable anticoagulant treatment during any periprocedural interruption of OAC (2,4). The present data were in accord with those of a previous study conducted by Ferreira et al., who demonstrated a low thromboembolic risk in a similar patient cohort using enoxaparin (14). In contrast to the scheme of Ferreira and colleagues, the present bridging regimen was not guided by frequent measurements of anti-factor Xa activity; rather, LMWH was administered following a pre-specified therapeutic scheme depending on the procedure's hemorrhagic risk and the patients co-morbidities. This approach provides a high practicability and offers the possibility for outpatient treatment.

Another important aspect of the present study was that patients with renal insufficiency were included, and treated with LMWH following individual therapeutic considerations. This was in contrast to the situation in previous studies, when patients with renal impairment and elder patients (aged >75 years) were excluded (15-18). Notably, approximately one-third of the present patients had evidence of renal insufficiency; this closely reflects daily in-hospital practice, where most patients with mechanical heart valves tend to be elderly with concomitant cardiovascular risk factors and important co-morbidities. Due to the renal excretion of LMWH, patients with renal impairment are at risk of anticoagulant accumulation, followed by

increased antithrombotic effects and a cumulative tendency to bleeding (21,22). Hence, in the present study, whilst the enoxaparin dose was halved in case of renal impairment, this approach did not lead to thromboembolism or major bleeding complications in these patients.

Study limitations

The real risk of thromboembolism during periprocedural 'short-term' interruption of OAC without anticoagulation in patients with mechanical valve replacement is not known. Current guidelines recommend bridging with either unfractionated or LMWH in high-risk patients with mechanical heart valves. However, assuming an annual thromboembolic rate of between 10 and 50% in patients with mechanical heart valves, and assuming that this risk is unaffected by the periprocedural bridging period (23), the present study lacks power to prove a significant risk reduction. In contrast, Gohlke-Bärwolf et al. highlighted a significant increase in thromboembolic events during the periprocedural period due to procedure-related altered hemostasis (increased platelet aggregation/activation, conversion of fibrinogen to fibrin, depressed fibrinolysis, etc.), to the prothrombotic effect of 'switching on and off' OAC, and to patient-related risk factors (4). This assumption was confirmed by the findings of Kovacs et al. (18) and Spyropoulos et al. (20).

The frequency of INR testing may have an influence on the good outcomes of the present study group, although in outpatients the measurements of INR were obtained at the discretion of the treating physicians. The outcome of these patients did not differ from that of patients treated in-hospital.

In conclusion, bridging therapy with enoxaparin in patients with mechanical heart valves following a standardized therapeutic approach was effective and relatively safe in a large cohort of patients. Therapeutic LMWH treatment seems to be an alternative to standard UFH therapy in this high-risk patient population with different co-morbidities, and may be the preferred option as its more convenient use can allow for outpatient treatment. However, minor bleedings are relatively common and a long duration of LMWH therapy seems to promote the incidence of hemorrhage. These data warrant that further large-scale studies should be conducted in order to determine the safety of bridging therapy with therapeutic dosages of LMWH in patients with mechanical heart valve replacement.

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