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Anticoagulant bridging in left-sided mechanical heart valve patients☆

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ABSTRACT

Background: In preparation for an invasive procedure with a high bleeding risk, patients with a mechanical heart valve temporarily have to discontinue their anticoagulant therapy and are usually bridged with either intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH). In this study we retrospectively analyzed the safety of UFH versus LMWH as bridging strategy in left-sided mechanical heart valve patients.
Methods: We performed a retrospective multicenter study in four surgical centers in The Netherlands. Patients with a mechanical heart valve implantation bridged from January 2010 until January 2015 were included. The cumulative incidence of adverse events in the 30 days following the procedure was recorded. Main outcomes were major bleeding according to International Society on Thrombosis and Haemostasis (ISTH) criteria, symptomatic thromboembolism, and mortality.
Results: In total, 238 (174 aortic, 42 mitral, 22 aortic + mitral) bridging episodes were included. The incidence of major bleeding was 16 (19%) events in the UFH group versus 29 (19%) events in the LMWH group ($p = 0.97$). Incidences of thromboembolism were 2 (2.4%) versus 1 (0.6%). The incidence of death was 1 (1.2%) patient in the UFH group versus 3 (1.9%) patients in the LMWH group. More than 50% of all bleeding complications were categorized as a major bleeding.
Conclusions: Bridging anticoagulation in patients with aortic and mitral mechanical valves is associated with considerable risk, but no difference was apparent between UFH and LMWH strategy. The rate of thromboembolism and death was low with either strategy and the vast majority of adverse events were bleedings.

1. Background

Patients with mechanical heart valves (MHV) are at increased risk of developing thromboembolic complications and require life-long administration of oral anticoagulants, i.e. vitamin K antagonists (VKA) [1–6]. In anticipation of an invasive procedure with a considerable bleeding risk, a temporary interruption of oral anticoagulation (OAC) may be required to reduce the increased periprocedural risk of bleeding [6–8]. In doing so, a fine balance must be reached between the risk of bleeding and the risk of developing thromboembolic complications. The VKA is stopped several days prior to the procedure to allow the effect to wane off [3,7]. During this time window consisting of sub therapeutic International Normalized Ratio (INR) levels, anticoagulation is continued using a short-acting heparin until and after the procedure [6,8–9]. If considered safe by the surgeon, the VKA is resumed shortly after the procedure and heparin is continued until a stable INR has been reached.

There are two strategies for heparin bridging; administration of intravenous unfractionated heparin (UFH), and subcutaneous low-molecular-weight heparin (LMWH) [6,9–10]. While both strategies reduce the risk of valve thrombus formation [11], they have distinct biomedical, financial [12–13], and logistical profiles. UFH is administered intravenously according to a nomogram and hence requires peri-procedural hospital admission and continuous monitoring of activated partial thromboplastin time (aPTT) [6,14]. In contrast, LMWH is administered subcutaneously once or twice daily in an outpatient setting and usually does not require continuous blood monitoring of anti-Xa levels [6,15–16].

Convincing evidence regarding the ideal heparinoid strategy is terms of efficacy and safety has not been established. As a result, no consensus regarding bridging strategy has been reached internationally. Current

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European Society of Cardiology (ESC) guidelines state that "*UFH remains the only approved heparin treatment in patients with mechanical prostheses*; *intravenous administration should be favored over the subcutaneous route* (*recommendation class IIa*, *level of evidence C*)" [9]. In contrast, American College of Cardiology/American Heart Association (ACC/AHA) guidelines advocate the use of either; "*bridging anticoagulation with either intravenous UFH or sub-cutaneous LMWH is recommended during the time interval when the INR is subtherapeutic preoperatively in patients who are undergoing invasive or surgical procedures with a 1*) *mechanical aortic valve replacement* (*AVR*) *and any thromboembolic risk factor*, *2*) *older generation mechanical AVR*, *or 3*) *mechanical mitral valve replacement* (*MVR*) (*Level of Evidence*: *C*)" [10]. Subsequently, hospital based protocols are frequently inconsistent with one another and the use of either UFH or LMWH is often left to the individual practitioner's discretion.

In this retrospective study we analyzed the clinical application of anticoagulant bridging in left sided MHV patients. In doing so, we assessed the safety and efficacy of UFH versus LMWH based on the cumulative incidence of adverse events, i.e. bleeding, thromboembolism, and death.

2. Methods

2.1. Data collection

Patients from 4 major surgical centers in The Netherlands with a mechanical AVR and/or MVR, bridged within the same hospital in the time period from January 1st 2010 until January 1st 2015 were included. Patients were included using databases provided by the participating hospitals and, where possible, the Dutch Thrombosis Center, Saltro. Bridging episodes were identified by scanning written patient documentation between January 2010 and January 2015. In case of uncertainty regarding bridging strategy, the medication list was consulted to identify any switch in anticoagulant medication, or laboratory measurements indicative of UFH strategy-specific aPTT values. Patients receiving sequential therapy (first UFH then LMWH, or vice versa) were included in an intention-to-treat analysis.

Patients with an incomplete bridging strategy, defined as no written documentation of anticoagulant bridging or no evidence of bridging in the patient's medication list or laboratory results, were excluded.

Subsequently patient records were searched for demographics, relevant comorbidities/risk factors for thromboembolic complications (atrial fibrillation, heart failure, diabetes mellitus, hypertension, malignancy, history of thrombosis) and bleeding (hypertension, history of bleeding), laboratory results, echocardiographic parameters (left ventricular ejection fraction, mitral valve stenosis, left atrial dimensions), medication history, details regarding the procedure, and adverse events.

Bridging protocols across participating centers were based on ESC or ACC/AHA guidelines. The UFH protocol consisted of cessation of anticoagulant therapy 3 (acenocoumarol) or 5 (fenprocoumon) days prior to the procedure. To monitor UFH efficiency, aPTT measurements were conducted every 6 h with subsequent heparin pump adjustments. LMWH dosages were given once or twice daily, adjusted according to body weight.

Adverse events were scored by two independent researchers (S.C. and J.W.), blinded to the bridging strategy. Any discrepancies were resolved by a third researcher (T.M.). Thromboembolic events were identified through written documentation and results from imaging. Bleeding was scored according to the International Society on Thrombosis and Haemostasis (ISTH) criteria [17–18]. The study protocol was reviewed and approved by the Medical Ethical Committee of the University Medical Center Utrecht.

2.2. Definitions

Definitions of adverse events are shown in the Supplemental Data Table 1. Any type of invasive procedure requiring anticoagulant bridging was included, estimated procedural bleeding risk was determined using bleeding risks reported earlier [19–20]. According to ISTH criteria, a major bleeding classification requires overt bleeding. In this study, we included a sub-category of patients that met criteria for a major bleeding yet in whom no overt bleeding was observed. High-risk MHVs were defined as mechanical mitral valves or aortic mitral valves with >1 risk factor for thrombosis (atrial fibrillation/flutter, left ventricular ejection fraction <35%, mitral stenosis, hypercoagulability, left atrial dilatation >50 mm, spontaneous contrast visible on echocardiography, previous thromboembolic event, older generation MHV (ball-in-cage, monoleaflet)).

2.3. Statistical analysis

Patients were stratified by bridging strategy for comparison of baseline characteristics. Continuous variables are expressed as mean ± standard deviation and compared using a Mann-Whitney *U* Test. Categorical variables are shown as numbers and percentages. Univariate analysis was performed using the Pearson chi-squared test or Fisher's exact test where appropriate. Differences were considered significant at a p-value < 0.05. All statistical analyses were performed using IBM SPSS Statistics Version 20.

3. Results

The study population consisted of 176 left-sided MHV patients that underwent a total of 238 bridging episodes. The baseline characteristics stratified by bridging strategy are outlined in Table 1.

The groups were comparable with respect to age, sex, thrombocyte count, creatinine level, bleeding risk, type of vitamin K antagonist, and medication. Furthermore, the prevalence of hypertension, malignancy, diabetes mellitus, and a history of arterial/venous thrombosis did not differ between the groups.

Mechanical aortic valves were primarily bridged with LMWH. High-risk mechanical heart valves were mostly bridged with UFH (61% versus 39% for LMWH). The prevalence of atrial fibrillation ($p < 0.01$) and heart failure ($p < 0.01$) was significantly higher in the UFH group compared to the LMWH group, although average CHA_2DS_2-VASc score was similar. The pre-procedural INR level was higher ($p < 0.01$) and the hemoglobin level was lower ($p < 0.01$) in the UFH group compared to the LMWH group. At baseline no difference was found in thrombocyte count. Follow-up on thrombocyte count was available in 110 bridging episodes (46%). In total, 1 patient the UFH group (1.2%) developed a >50% drop from baseline in thrombocyte count, compared to 5 patients (3.2%) in the LMWH group. No specific laboratory analysis for heparin-induced thrombocytopenia was available.

In total 44 out of 176 patients (25%) were bridged more than once in the 5-year time period. Nine (5.1%) of these patients underwent a different bridging strategy (UFH or LMWH) during the second or third bridging episode. Missing values were recorded as follows: body mass index (UFH 17; LMWH 40), INR (UFH 12; LMWH 27), hemoglobin (UFH 8; LMWH 48), thrombocyte count (UFH 9; LMWH 64), creatinine (UFH 3; LMWH 15), vitamin K antagonist (UFH 1; LMWH 1), LVEF (UFH 50; LMWH 104), mitral valve stenosis (UFH 50; LMWH 104), left atrial dilation > 50mm (UFH 50; LMWH 104).

3.1. Incidence of adverse events

In Table 2 the cumulative incidences of major adverse events (major bleeding, thromboembolism, and death) within 30 days following the procedure are displayed.

No statistically significant differences between the groups were observed. In total, 19 procedures (23%) bridged with UFH experienced an adverse event compared to 33 procedures (21%) bridged with LMWH ($p = 0.83$). With regards to bleeding, a major bleeding occurred in 19% of patients in both bridging groups.

A clinically relevant non-major bleeding (CRNMB) occurred in 9.5 and 13% of patients for UFH and LMWH respectively. A minor bleeding was observed in 1.2 and 4.5%, and a major bleeding without overt bleeding in 4.8 and 2.6%. Four patients died, 1 of which was bridged with UFH and 3 with LMWH. A thromboembolic event occurred in 2 patients bridged with UFH and in 1 patient bridged with LMWH.

All thromboembolic complications were preceded by a bleeding event. Treatment of these bleeding events included correction of the anticoagulant therapy. Three-out-of four deaths were bleeding related. In these patients the bleeding episode and thromboembolism or death were recorded as two independent adverse events.

3.2. Evaluation of bleeding events

Among bleeding events, in retrospect 45 (51%) were judged as a major bleeding, 28 (31%) a CRNMB, and 8 (9%) a minor bleeding. Eight (9%) events were judged as a major bleeding without overt bleeding.

Major bleedings are outlined in the Supplemental Data Table 2. Among major bleedings, 16 (36%) were bridged with UFH versus 29 (64%) with LWMH. The majority of procedures were of high bleeding risk. Nearly one-quarter (24%) of all major bleedings in the LMWH group consisted of macroscopic hematuria, while no hematuria was

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