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Full Length Article

Prophylactic doses of low-molecular weight heparin as periprocedural bridging therapy in mechanical heart valve patients

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ABSTRACT

Background: Mechanical heart valve (MHV) patients undergoing invasive procedures necessitating an interruption of their lifelong anticoagulant therapy, often require bridging with low-molecular weight heparin (LMWH) or unfractionated heparin. The aim of this study was to assess whether bridging MHV patients with prophylactic doses of LMWH undergoing invasive, elective procedures is a safe and effective method.

Method: This observational cohort study included all MHV patients on vitamin K anticoagulant therapy in Malmö, registered and monitored via AuriculA (the Swedish national quality registry for atrial fibrillation and anticoagulation), between 1/1/2008 and 31/12/2011. Inclusion criteria were periprocedural bridging therapies conducted via AuriculA. Primary endpoints were mortality, thromboembolic (TE) events or major bleedings (MBE) within 30 days of bridging.

Results: During the study period, 210 patients had undergone 434 bridging therapies managed via AuriculA; 203 due to subtherapeutic INR-values were excluded. The remaining 231 periprocedural bridging therapies were included. All were bridged with prophylactic doses of LMWH. When comparing patients with aortic and/or mitral valve replacements undergoing low- or high-risk interventions, only number of days bridged for a low-risk intervention differed significantly. Patients with a mitral or mitral and aortic valve replacement were bridged for a longer period ($p = 0.023$). No TE events, 1 death (0.4%) and 3 MBEs (1.3%) occurred related to periprocedural bridging.

Conclusion: Our study shows a low rate of MBEs, deaths and no TE events when bridging MHV patients undergoing invasive, elective procedures with prophylactic doses of LMWH.

1. Introduction

When a patient with a mechanical heart valve (MHV) is in need of surgery or an invasive procedure, an interruption of their lifelong anticoagulation therapy might be necessary. An interruption of the vitamin-K antagonist (VKA) therapy results in a subtherapeutic International Normalised Ratio (INR) - value, significantly increasing the risk of thromboembolic (TE) events. Current guidelines recommend conducting what is known as a bridging therapy or procedure as a means to reduce this increased risk [1–3].

European as well as American guidelines recommend not interrupting VKA-therapy for most minor procedures. However, further recommendations regarding when, how and if to conduct a bridging therapy differ. European guidelines state that major surgeries requiring an INR-value < 1.5 necessitates a withholding of VKA-therapy. Subsequent bridging with unfractionated heparin (UFH) intravenously, or therapeutic doses of low molecular-weight heparin (LMWH) is recommended, though stating that the use of LMWH is not approved in patients with MHVs [3]. According to American guidelines, patients should be categorised based on valve position, type of prosthesis and other risk factors for TE if a surgery require VKA-interruption. Recommended bridging regimen is either UFH or therapeutic doses of LMWH, further stating that patients with an isolated aortic bileaflet prosthesis (AVR) and no other risk factors do not require bridging [1,2].

There are significant limitations in the evidence constituting the current guidelines, which are all based on evidence level C. There are also significant limitations in the existing studies and reviews comparing or assessing the overall safety and complications related to bridging MHV patients [4–12]. These include differences in bridging regimens, unclear basis for choosing a particular regimen, and size of

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the cohorts. This creates uncertainty in terms of optimal bridging strategy for the estimated 4 million people worldwide with prosthetic heart valves and if bridging is necessary in all cases [13]. There is also a current lack of studies evaluating a prophylactic bridging approach and potential benefits of such a regimen. Therefore, this study aims to assess whether bridging MHV patients with prophylactic doses of LMWH undergoing invasive, elective procedures is a safe and effective method, through retrospective analysis of MHV patients in Malmö, Sweden.

2. Method

2.1. Study design

This population-based study retrospectively analysed MHV patients undergoing bridging therapies at the University Hospital in Malmö between 1/1/2008 and 31/12/2011. All MHV patients on oral anticoagulation treatment registered and monitored prospectively via the Swedish national quality registry for atrial fibrillation and anticoagulation, AuriculA, were included in the study. AuriculA is a registry including a web-based dosing program and decision support, which uses an algorithm to calculate the warfarin dosage based on the last two INR results.

Inclusion criteria were that the periprocedural bridging was planned by the physicians and/or nurses at the coagulation centre in Malmö, via AuriculA. Exclusion criteria were bridging therapies not related to a procedure, due to emergency interventions or if planned by the treating physician and not via AuriculA, as well as bridging therapies being due to a planned heart valve surgery or CABG operation since these surgeries are in themselves associated with high risk of TE and bleeding. Bridging related to cardiothoracic surgeries are commonly managed by the treating cardiothoracic surgeon or cardiologist, usually with therapeutic doses of LMWH or UFH. Any complications occurring within 30 days of the aforementioned procedures were not included.

During the study period, all patients had a target INR-interval of 2.0–4.0, irrespective of valve position. A bridging episode was initiated by the nurses at the Coagulation centre according to a prespecified protocol in the event of an elective surgery or procedure, as well as in some cases of patients having subtherapeutic INR-values for other reasons.

If needed, the nurses consult one of the physicians at the centre for suitable strategy. Details regarding bridging were registered prospectively. Data concerning INR-values, indication for bridging, type, dosage and number of days bridged and pre- and postprocedural days of not receiving warfarin was extracted from AuriculA by one of the authors. An annual survey of major complications, i.e. stroke/TIA or major bleeding, is performed and registered in AuriculA by the nurses. All events registered and included in this study were retrospectively validated by one of the authors, who evaluated the complete medical records to confirm the diagnosis and identify further complications.

Details regarding type of procedure, bridging strategy in relation to the procedure and INR-value at the time of the procedure, were collected from hospital records. The invasive procedures were categorised into low- or high-risk procedures, according to the Swedish Society on Thrombosis and Haemostasis' risk-categorisation [14]. If a procedure could not be found in neither AuriculA nor the medical records, it was categorised as low-risk.

2.2. Study definitions

Demographic data such as age, gender and position of the MHV was extracted from AuriculA. The hospital records were examined for a large number of baseline characteristics and demographics.

A prophylactic dose of LMWH was defined as 40 mg of enoxaparin daily, 5000 International Units (IU) of dalteparin daily, or 3500–4500 IU tinzaparin daily. Therapeutic doses of LMWH were defined as enoxaparin at least 1 mg/kg daily, dalteparin 200 IU/kg or tinzaparin 175 IU/kg daily [1].

Primary safety endpoints were mortality, major bleeding and TE events. A major bleeding event (MBE) was defined according to guidelines from the International Society on Thrombosis and Haemostasis (ISTH) and included fatal bleeding, symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, intramuscular with compartment syndrome), extra surgical site bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to a transfusion of two or more units of whole blood or red cells, surgical site bleeding that requires a second intervention, surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability [15]. Guidelines for reporting mortality and morbidity after cardiac valve intervention were used to define TE events [16]. These definitions for TE include stroke, transient ischemic attack or an embolus documented operatively, at autopsy, or clinically that produce signs or symptoms attributable to complete or partial obstruction of a peripheral artery. An event occurring within 30 days of the bridging therapy was considered potentially associated with bridging.

If a bridging therapy due to an invasive procedure required a prolonged bridging period, with a restart of LMWH-treatment after the scheduled period had ended, it was considered a consequence of the interruption of VKA treatment and therefore included in the intervention-related bridging therapy and not as a new episode of bridging for subtherapeutic INR-values.

Patients were further subdivided based on valve position and patients with a mitral valve replacement (MVR) or an AVR and an MVR (from here on referred to as “MVR/combined”) were categorised together due to similar valve-related risk for TE events.

Written consent was obtained from the patients, none refused participation. The study was approved by the Regional Ethical Review Board in Lund (EPN 2012/130).

2.3. Statistical analysis

Continuous variables with normal distribution are presented as means with standard deviation (SD). If continuous variables were found to have skewed distribution, they are presented as medians with interquartile ranges (IQR). Categorical variables are described as frequencies and percentages. When comparing variables, Fisher's exact test was used for categorical variables and *t*-test or Mann-Whitney *U* test were used for continuous measures, as appropriate. A p-value < 0.05 was considered to indicate statistical significance. The rate of adverse events within 30 days of a bridging therapy was described using cumulative incidence. No formal hypothesis testing was performed due to the low rates of adverse events. The data was analysed with IBM SPSS statistics version 22.

3. Results

3.1. Study population

There was a total of 407 patients with MHVs on oral anticoagulation therapy, registered and monitored via AuriculA between 1/1/2008 and 31/12/2011. Of these, 210 patients had undergone a bridging episode planned via AuriculA during the study period. Eighty patients had been bridged due to subtherapeutic INR-values not related to a procedure and were excluded. The remaining 130 patients were included.

There were significantly fewer men in the MVR/combined group compared to the AVR-group ($p = 0.0021$). Patients in the MVR/combined more frequently had atrial fibrillation ($p = 0.0097$). No other statistically significant differences were found between valve groups.

Patient characteristics are presented in Table 1.