Perioperative bridging of chronic oral anticoagulation in patients undergoing pacemaker implantation—a study in 200 patients

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Objective To assess the risk of bleeding and thromboembolism (TE) of bridging therapy with low molecular weight heparin (LMWH) in patients undergoing pacemaker implantation.

Background Current guidelines on peri-procedural management of patients with chronic oral anticoagulation (OAC) give no explicit recommendations on how to treat patients undergoing pacemaker implantations.

Methods and Results Since 2000 all patients with chronic OAC undergoing pacemaker implantation were prospectively enrolled and treated following a pre-specified bridging regimen with enoxaparin using reduced LMWH doses in patients at non high TE risk and renal impairment. Patients were followed up for 30 days regarding bleeding complications, incidence of thromboembolism, length of therapy and adverse events following bridging therapy. 200 patients (age 78.4 ± 8.3 years; 60.5% male) were enrolled and treated with enoxaparin for a mean of 7.3 ± 4.2 days. 109 patients (54.4%) were assigned to high TE risk and 91 (45.6%) to non high TE risk. Renal insufficiency (CrCl of <50 ml/min) was present in 92 patients (46%). After risk stratification 72.5% of patients (n = 145) were treated with reduced LMWH doses. Outpatient treatment was feasible in 39 patients (19.5%). Nine bleeding complications were observed (4.5%; 95% confidence interval [CI] 2.1–8.4%), including one major bleed (0.5%; 95% CI 0.01%–2.75%) and eight minor bleeds (4%; 95% CI 1.74%–7.73%). No thromboembolic complications evolved due to bridging therapy (0%; 95% CI 0.0–1.49%). After multivariate regression analysis independent predictors for bleedings were the development of thrombozytopenia (hazard ratio [HR] 6.0, 95% CI 0.3–139.8; P = 0.002), the prevalence of congestive heart failure (HR 4.5, 95% CI 0.9–22.2; P = 0.01), high TE risk (HR 6.9, 95% CI 1.9–25.6; P = 0.03) and an increasing CHADS2 score (HR 2.3, 95% CI 1.0–5.4; P = 0.05).

Conclusion Oral anticoagulation can be safely interrupted before pacemaker implantation under overlapping therapy with enoxaparin. Reducing heparin doses in patients with low thromboembolic risk and renal insufficiency led to a low incidence of major bleeding without increasing thromboembolic events.

Keywords Oral anticoagulation • Bridging therapy • Pacemaker implantation • Low molecular weight heparin • Risk stratification

Introduction Up to 45% of patients undergoing pacemaker implantation procedures receive chronic oral anticoagulation (OAC) with Vitamin K antagonists (VKA).1 Since the current guidelines give no explicit information how to manage such patients2–4 the optimum peri-operative anticoagulant regimen is still on debate.5–7 Evidence from current literature indicates that peri-procedural therapy with intravenous application of high heparin doses increases the risk of clinically relevant pocket haematoma.8 On the other hand performance of surgery under continued OAC bears a relevant risk for bleedings since VKAs’ half life
ranges between 24 to 72 h with relevant differences in individuals’ response to this therapy.9,10 There is still an unmet need for the evaluation of safe and feasible treatment options in patients with OAC undergoing pacemaker implantations.11

The aim of the BRAVE registry (Bonn Registry for Alternative peri-procedural Anticoagulation to Prevent Vascular Events) is to document, prospectively, the risk of bleeding and thromboembolism and to assess the length of bridging therapy, following a standardized LMWH bridging regimen in patients under OAC who require surgery or an invasive procedure with need for interruption OAC therapy. In this paper, we report the results of bridging non-pregnant patients undergoing pacemaker implantations.

**Methods**

**Patients**

Details of the Bonn Registry of Alternative Anticoagulation to Prevent Vascular Events (BRAVE) have been published elsewhere.12,13 Briefly, eligible patients were recruited for participation consecutively in the years from 2000 until the end of 2008. The following inclusion criteria applied: patients aged 18 years or older, require bridging therapy with enoxaparin (Clexane®, Lovenox®, manufacturer: sanofi-aventis, Berlin) owing to interruption of OAC because of surgical or other intervention with elevated bleeding risk. The following exclusion criteria were observed: interruption of OAC for more than one month prior to inclusion in the register; body weight <45 kg; life expectancy <2 months; cerebral or gastrointestinal bleeding within the previous six months; known allergy to UFH or LMWH; history of heparin-induced thrombocytopenia (HIT II) or current thrombocytopenia; current neurological deficit or embolism; chronic liver disease; severe chronic renal failure with CrCl<20 ml/min; endocarditis; pregnancy; known coagulation disorders.

At the initiation of the study, owing to its observational type neither an ethical approval procedure nor signed patient informed consent were stipulated by the German Drug Law or by regulatory bodies.14 However, before study participation all patients were informed by the investigators about the aims and scope of the register and the fact that participation did not change the treatment in any way. All patients had to provide written informed consent for data collection and analysis.

**Documentation**

The following parameters were documented on standardised case report forms: initials, sex, bridging duration, concomitant diseases (arterial hypertension, coronary heart disease, diabetes mellitus, chronic heart failure, history of arterial embolism) and creatinine clearance. Individual TE events of the patients were documented in line with previous studies.15–17

Adverse events were defined as follows: death, TE, thrombocytopenia (no HIT) and bleeding (major and minor bleeding). Thrombocytopenia was defined as a decrease of more than 50% of the value prior to LMWH, or a decrease <100 000.

The data were entered by trained personnel at the inclusion of the patient in the study, and 30 days after the intervention on the basis of the patient files or after telephone consultation with the family physician or the patient himself (follow-up).

**Risk stratification**

Patients were stratified to be at high TE risk in presence of:

- Mechanical valve replacement
- Deep vein thrombosis or pulmonary embolism within 3 months before enrolment
- Atrial fibrillation
- More than two concomitant risk factors (diabetes, arterial hypertension, age >75 years)
- Echocardiographically proven left atrial thrombus-formation and/or dense spontaneous left atrial echo-contrast;
- History of thromboembolism;
- Chronic heart failure with left ventricular ejection fraction <35%.

All other patients were classified at non high TE risk. Individual risk stratification was predominantly determined by concomitant clinical risk factors. Transthoracic and transoesophageal echocardiography was performed if clinical risk stratification was ambiguous.

Additionally, the CHADS2 score was determined in all our patients and subsequently analyzed, this score consists of Congestive heart failure (1 point), Hypertension (untreated or treated, 1 point), Age >75 years (1 point), Diabetes (1 point), Prior Stroke or TIA (2 points).

**Peri-procedural anticoagulation**

Bridging therapy was conducted following a pre-specified, risk adapted regimen which has been established at the author’s institution since the year 2000 (Figure 1):

Four to six days before the procedure, treatment with phenprocoumon was interrupted; INR was measured daily 48 h after interruption of OAC. When INR fell below 2, the patients received bridging therapy with enoxaparin following a standardized therapeutic scheme. Patients at high TE risk were administered subcutaneous enoxaparin 1 kg/kg twice daily, patients at non high TE risk and patients with renal impairment (defined as calculated Cr Cl 20–50 ml/min according to Cockcroft Gault formula18) were treated with enoxaparin in half-therapeutic dosage (1 mg/kg once daily). Surgery was performed at an INR of <1.5 and enoxaparin therapy was withheld on the evening before the procedure (at minimum for 24 h before surgery). Enoxaparin was restarted not shorter than 24 h after pacemaker implantation with concomitant OAC. During interruption of high dose LMWH therapy, enoxaparin was administered following the dosing requirements for thrombosis prophylaxis.

**Endpoints**

The primary safety endpoint was the incidence of overall bleeding complications. All haemorrhages were categorized using modified GUSTO and TIMI classifications.19,20 Major bleeding was defined as bleeding requiring acute treatment/re-surgery, medical evaluation, or transfusion with at least 2 units of blood; intracranial haemorrhage or retroperitoneal haemorrhage; need for prolonged hospitalization; and all fatal and life-threatening bleeding. Minor bleeding was defined as all other types of bleeding, including haematoma of >5 cm at the LMWH injection site or prolonged bleeding at the section site. The primary efficacy endpoint was the incidence of thromboembolic complications, defined as clinical signs of stroke, transient ischaemic attack, arterial embolism or myocardial infarction due to coronary embolism. Secondary endpoints were length of LMWH-therapy, incidence of HIT, thrombocytopenia due to other causes, and any other adverse events following LMWH-therapy.

Length of bridging therapy was defined as time [days] with ineffective INR and need for heparin-treatment.

Outpatient treatment was defined as discontinuation 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.
Statistics
Results are shown in natural units. Categorical variables are reported as frequencies and relative frequencies (percentages). For continuous variables number of patients, mean and standard deviation (SD) were provided. In case of comparison between groups, 2-tailed t tests were used; in case of comparisons within groups 2-tailed paired t tests were used. For the event rates 95% confidence intervals were provided using the method of Blyth-Still-Casella. Univariate logistic regression analysis was used to describe the prognostic value of single parameters for the prediction of bleeding complications under bridging therapy. A variable was selected for further multivariate analysis if the level of significance in univariate logistic regression was ≤ 0.2.

Data were prospectively collected and analyzed using SPSS for Windows (PASW statistic., Version 17.0.2, SPSS Inc., Chicago, Illinois, USA) and MedCalc statistical software (MedCalc Software, Version 11.4.1.0, Mariakerke, Belgium).

Endpoints
Of the 200 patients evaluated, we observed nine bleeding complications (4.5%; 95% confidence interval [CI] 2.1–8.4%) including one major bleed (0.5%; 95% CI 0.01%–2.75%), which was a haemodynamically relevant haemorrhagic pericardial effusion which required open heart surgery with re-implantation of the ventricular pacemaker lead.

Minor bleeds occurred in 8 patients (4%; 95% CI 1.74%–7.73%), including haematoma of >5 cm at the LMWH injection site or surgical wound. One pocket haematoma was observed after pacemaker implantation (0.5%) which was treated conservatively, without need for surgical revision or prolonged hospitalization (Table 2, details of bleeding complications). No thromboembolic complication evolved due to bridging therapy (0%; 95% CI 0.0–1.83%) (Table 3).

The mean treatment duration was 7.3 ± 4.2 days. Patients at high TE risk received bridging therapy with enoxaparin for a mean of 7.7 ± 4.3 days, patients at non high TE risk for a mean of 6.9 ± 4.0 days (P = 0.19). 39 patients (19.5%) were treated as outpatients. Thrombocytopenia was observed significantly more often in high risk patients (7.7%, 1.8%; P = 0.05) which received higher cumulative doses of enoxaparin defined as mg/kg body weight, calculated from enoxaparin dosage per day and duration of LMWH therapy (17.1 ± 68.3 mg/kg, 8.0 ± 15.2 mg/kg; P < 0.0005). Laboratory testing and clinical examinations excluded heparin induced thrombocytopenia type II in all cases. Echocardiography at the beginning and end of bridging therapy excluded valvular thrombosis in patients with AF and mechanical valve replacement (Table 3).

Haemorrhagic risk factors
Subsequent statistical analysis revealed that independent from single risk factors like renal function, BMI, and daily or cumulative enoxaparin dosage the incidence of haemorrhagic complications was significantly elevated in patients categorized at high TE risk.
as compared to patients categorized at non high TE risk (7.3%, 1.1%; \( P = 0.04 \)) (Table 3). Univariate and subsequent multivariate logistic regression analysis identified an increasing CHADS$_2$ score, high TE risk, congestive heart failure and occurrence of thrombocytopenia as independent predictors for haemorrhages (Table 4).

## Discussion

The main findings of our study are that patients with OAC can safely undergo pacemaker implantation under bridging therapy with enoxaparin following a risk adapted anticoagulant regimen with reduced enoxaparin doses in patients with non high TE risk and in presence of renal impairment. This is the first study to show that dose reduction of LMWH after individual risk stratification led to a low incidence of major bleedings and/or pocket hematoma without increasing thromboembolism in such patients. This approach may be helpful in daily practice since LMWH administration can be performed in an outpatient setting and risk stratification follows simple demographic variables and determination of renal function from serum creatinine.

### Current guidelines

Current guidelines state that interruption of OAC is mandatory before interventions at elevated risk of bleeding.\(^{21-24}\) In patients with relevant TE risk alternative anticoagulation with heparins is...
advised to reduce the risk of thromboembolism when OAC is ineffective. Since published evidence on this clinical relevant topic is scarce, available national and international guidelines are in part incoherent and only limited data are available for specific surgical or non-surgical interventions. The optimum peri-procedural anticoagulant regimen for patients with non high TE risk and/or interventions with intermediate risk of bleeding is still on debate. Despite up to 45% of patients undergoing pacemaker implantation procedures receiving OAC,1 it remains unclear how such patients should be treated. Current guidelines state that in some cases pacemaker may be safely implanted under continued OAC, but in other cases bridging OAC with heparins might be a reasonable approach and a definite statement is not possible.

Available evidence

Several studies investigated the outcomes of patients with OAC undergoing pacemaker or ICD-implantation by comparing two therapeutic approaches (a) performance of the intervention under continued OAC and (b) interruption of OAC under bridging therapy with high doses of heparins. Generally the risk of pocket haematoma ranges between 5–8% if pacemaker implantation is performed under full anticoagulation with either heparin or VKA and increases with concomitant use of antiplatelet therapy up to 20–25%.7 Interestingly, some data indicate an elevated risk for pocket haematoma in patients who undergo pacemaker implantation under continued OAC whilst others showed that peri-procedural treatment with high doses of heparin may increase the risk of bleedings relevantly.25 On the other hand, there is evidence that the difference between both therapeutic options is statistical not significant.26 In a recent meta-analysis of these studies11 the authors stated, that the perioperative management of such patients is not established, but therapy with high doses of intravenous UFH confers a high risk for bleedings.

In the presented study we included 200 patients undergoing pacemaker procedures which were treated with enoxaparin after interruption of OAC following a pre-specified therapeutic approach. This is the first study aiming to investigate the safety and efficacy of using reduced LMWH doses in patients considered at non high TE risk or in presence of renal dysfunction. When

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CI, confidence interval; TE, thromboembolic; HIT, heparin induced thrombocytopenia.
comparing our results to the cited studies, this approach seems to reduce haemorrhages as compared to bridging patients with high doses of heparins or under continued OAC without increasing the risk of thromboembolism.

**Risk stratification**

Since perioperative risk of patients depends on varying individual and procedural factors increasing either the risk for TE or bleedings, it is difficult to develop a unique therapeutic approach fitting for all presenting cases. In common practice patients are treated with either full doses of heparins or interventions are performed under continued OAC. Up to now no study has investigated the safety of reducing heparin doses for bridging OAC following individual risk stratification. In contrast to VKA, which are ineffective for thromboprophylaxis when INR drops below 1.7, anticoagulant effect of different LMWHs is dose dependent, but reduced LMWH doses still effectively prevent thrombotic events. LMWHs may accumulate in patients with relevant renal insufficiency; therefore dose reduction is advised in those patients.

Our bridging strategy includes two important clinical considerations: (i) Dose reduction of enoxaparin in patients with non high TE risk, whose clinical outcome is predominantly driven by the occurrence of bleeding complications. (ii) Dose reduction of LMWH in patients with renal insufficiency after estimation of renal function following the Cockroft Gault formula. Furthermore, to decrease the risk of clinical relevant bleeding complications, we withheld LMWH therapy for at least 24 h before and after pacemaker implantation (Figure 1). When comparing our results with the cited studies, this approach seems effective to reduce the incidence of haemorrhages; clinical relevant bleedings and pocket haematoma in particular were rare. Nevertheless, haemorrhages occurred predominantly in patients considered at high TE risk or with increasing CHADS₂ score. This might be due to the fact, that haemorrhagic and TE risk factors are almost the same, and of course the attending physician’s tendency to treat patients at high TE risk with higher doses of heparins.

**Limitations**

Although this registry was conducted prospectively, there might be a decision-bias, when the physician chooses to treat a patient with LMWH, following our pre-specified bridging-regimen or to choose so-called standard-therapy with UFH. We cannot exclude that multi-morbid patients or those with a very high incidence of co-morbidities were set on UFH treatment and therefore preliminarily excluded from participation in this registry, which may reduce the incidence of complications under LMWH-therapy. Furthermore, this is a single arm study, without randomization into different therapeutic arms; hence, it is possible that another anticoagulant therapy would reach equal preferable results. Nevertheless, due to current international treatment guidelines on anticoagulant therapy and published data sets on this subject, it seems impossible to conduct a placebo-controlled trial on bridging therapy in the future. Additionally, a prospective-randomized study, comparing a “new” treatment strategy with LMWH with so-called “standard therapy” with UFH would be difficult to conduct because the number of patients that must be included to reach statistical significance would be very high.

Following our bridging regimen the incidence of bleedings was very low. After multivariate analysis bleedings occurred more frequently in patients considered at high TE risk whilst other classical risk factors were not associated with an elevated risk of bleeding. Diminishing the periprocedural risk in high risk patients is still crucial. Since the expected rate of thromboembolic events even without bridging therapy during short term interruption of OAC is very low, this study alone does not prove the efficacy of half dose LMWH in patients with renal insufficiency or at low TE risk in terms of avoiding ischaemic events.

**Conclusions**

Oral anticoagulation can be safely interrupted before pacemaker implantation under overlapping therapy with low-molecular weight heparin. Reducing heparin doses in patients with low thromboembolic risk and renal insufficiency led to a low incidence of major bleeding without increasing thromboembolic events.

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**References**


