

## Original Article

# Anticoagulation management of patients with long-term warfarin therapy after valve replacement during the perioperative period of pacemaker implantation

Zhi-Hong Han, Xue-Jun Ren, Ye Wang

*Department of cardiology, Institute of Heart Lung and Blood Vessel Disease, Beijing Anzhen Hospital Affiliated to Capital Medical University, Beijing 100029, China*

Received June 4, 2013; Accepted July 15, 2013; Epub August 1, 2013; Published August 15, 2013

**Abstract:** Background: To explore an optimal management of perioperative anticoagulation for patients with long-term warfarin therapy after valve replacement during the perioperative of pacemaker implantation. Methods: We retrospectively reviewed consecutive patients undergoing pacemaker implantation who received long-term warfarin therapy after valve replacements at our hospital. They were divided into 3 groups: discontinued group, bridging group and continued group. We analyzed the relationship between different anticoagulation methods during the peri-procedure period and hemorrhage and embolism events. Results: 132 patients were enrolled. There was no significant difference concerning the mean age, sex, concomitant diseases, atrial fibrillation and whether performed pacemaker replacement among 3 groups. The incidence of hematomas was irrespective of the perioperative anticoagulation strategy used ( $P = 0.125$ ). A strategy involving bridging anticoagulation with therapeutic-dose heparin was associated with an incidence of wound dehiscence ( $P = 0.008$ ). There was no thromboembolism event in these three groups. Conclusion: The results showed that there was no significant difference in hematoma rate among continued group, discontinued group, and bridging group, but there was much more wound dehiscence in the bridging group. Also, the study shows that if warfarin is continued, it will not increase the risk of bleeding when the International Normalized Ratio (INR) is around 1.7 during the procedure.

**Keywords:** Cardiology, pacemaker, anticoagulation, valve replacement, hematomas, thromboembolism

## Introduction

Clinically, there is an urgent need for better management of long-term oral warfarin therapy in patients with mechanical heart valve(s) and in need of implantation of pacemaker. Considering the risk of bleeding, the surgery is usually postponed until international normalized ratio (INR) dropped to near normal level, however, it would increase the risk of thromboembolism. Currently, guideline recommends that such patients receive therapeutic doses of intravenous heparin or subcutaneous low molecular weight heparin as bridging therapy [1]. However, bridging therapy can increase the risk of pouch bleeding and other bleeding complications increase the difficulty of surgery and related costs, and even prolonged hospital stay. Therefore, some researchers have begun to explore the feasibility of continuing warfarin

therapy in such patients during the perioperative period of pacemaker implantation. But the safety of this treatment needs to be further confirmed, which would be discussed in this study.

## Methods

**Ethics Statement:** We obtained the data from Patients Information Department in Beijing Anzhen Hospital Affiliated to Capital Medical University. All patients provided written informed consent for both the procedure and subsequent data collection and analysis for research purposes. The study was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Anzhen Hospital Affiliated to Capital Medical University. There was no industry involvement in the design, conduct, financial support, or analysis of the study.

## Anticoagulation management of patients with pacemaker

**Table 1.** Clinical Characteristics of Patients with Different Anti-coagulation Method

	Discontinued Group (n = 40)	Bridging Group (n = 58)	Continued Group (n = 34)
Age	61.0 ± 6.3	59.1 ± 8.6	62.9 ± 8.6
Male	20 (50.0)	32 (55.2)	16 (47.1)
Valve Replace Procedures*			
MVR	27 (67.5)	27 (46.6)	17 (50.0)
AVR	6 (15.0)	4 (6.9)	9 (26.5)
DVR	7 (17.5)	26 (44.8)	8 (23.5)
Concomitant Disease	28 (70.0)	32 (55.2)	24 (70.6)
HT	16 (40.0)	15 (25.9)	14 (41.2)
DM	2 (5.0)	6 (10.3)	0
HT + DM	2 (5.0)	7 (12.1)	0
CAD	8 (20.0)	0	4 (11.8)
Others	0	4 (6.9)	6 (17.6)
AF	31 (77.5)	41 (70.7)	22 (64.7)
Paroxysmal	6 (15.0)	8 (13.8)	7 (20.6)
Persistent	25 (62.5)	33 (56.9)	15 (44.1)
Pacemaker Replacement	6 (15.0)	10 (17.2)	6 (17.6)
Single-Chamber Pacemaker*	32 (80.0)	48 (82.8)	18 (52.9)

Valve surgery method: MVR = mitral valve replacement; AVR = aortic valve replacement; DVR = mitral + aortic (Double) valve replacement surgery; Concomitant disease: HT = Hypertension; DM = Diabetes Mellitus; CAD = Coronary Artery Disease.

\*Comparison among the three groups, P <0.05.

### Study objects and groups

The study was retrospective. It assessed patients who had received device implantation after operation of mechanical valve replacement and were on long-term oral warfarin therapy.

According to perioperative anticoagulation methods, the patients were divided into three groups shown in **Table 1**: (1) Anticoagulation discontinued group (n = 40): Warfarin was discontinued 3 to 5 days before implantation or vitamin K was prescribed to adjust the INR to normal range. Only when INR <1.5 was the device implantation performed. After the surgery, warfarin was reinstated at night; (2) Bridging group (n = 58): Warfarin was stopped or not 12 ~ 18 hours before the surgery, and patients received pre- and post-operative bridging with therapeutic dose of low molecular weight heparin subcutaneously and received device implantation when INR <1.5; (3) Continued warfarin group (n = 34): Continue warfarin therapy throughout the whole procedure and maintain the INR within the therapeutic range (1.5 to 2.5).

### Study methods

This is a retrospective study. Age, gender, name of the valve surgery, concomitant diseases,

anticoagulation method, and dosage of warfarin during surgery, preoperative and postoperative INR values, postoperative wound hemorrhage, and postoperative hospital stay of all the enrolled patients were recorded. The relationship between different anticoagulation methods and the risk of bleeding and embolic events during hospitalization were analyzed.

### Statistical analysis

All study data were analyzed by SPSS 13.0 software package. The measurement data of normal distribution were expressed as mean ± standard deviation, and the count data were expressed as case number (percentage). The comparison among different groups was conducted by one-way ANOVA test. A P Value <0.05 was considered Significant.

### Results

#### General clinical condition

132 patients were enrolled in the study, in which 68 cases were male (51.5%), 64 cases were female (48.5%). Age was 60.6 ± 8.1 years old. Name of valve surgery: 61 cases (50.0%) accepted mitral valve replacement, 19 cases (15.6%) accepted aortic valve replacement, 41

## Anticoagulation management of patients with pacemaker

**Table 2.** INR level, Perioperative Hemorrhage and Post-operative Hospital Stay

	Discontinued Group (n = 40)	Bridging Group (n = 58)	Continued Group (n = 34)
Hematoma	1 (2.5)	6 (11.3)	0
Wound oozing	1 (2.5)	14 (24.1)	2 (5.9)
Pre-operative INR	1.30 ± 0.23	1.27 ± 0.22	1.74 ± 0.21
Post-operative INR	1.18 ± 0.31	1.18 ± 0.19	1.70 ± 0.38
Post-operative Hospital Stay	8.0 ± 2.2	9.2 ± 4.2	8.1 ± 2.8

\*Comparison among three groups, P <0.05.

cases (33.6%) accepted mitral and aortic valve replacement, and 1 case (0.8%) accepted tricuspid valve replacement. In these patients, 84 cases (68.9%) had concomitant diseases, including hypertension in 45 cases (36.9%), diabetes mellitus in 8 cases (6.6%), hypertension and diabetes mellitus in 9 cases (7.4%), coronary artery disease in 12 cases (9.8%), and other diseases in 10 cases (8.2%). 94 cases (77.0%) were atrial fibrillation (AF), including 21 cases (17.2%) paroxysmal atrial fibrillation patients and 73 cases (59.8%) persistent AF patients. 22 cases (18.0%) accepted device replacements.

In these three groups, there were no difference in patients' age, gender, concomitant diseases, atrial fibrillation, or whether performed pacemaker replacement, except for the name of valve surgery and the type of pacemaker.

### *Comparison of three groups in complications, INR, and hospital stay*

The use of warfarin after surgery: In discontinued group, warfarin was started from the 2<sup>nd</sup> ~ 9<sup>th</sup> day. In most cases, warfarin was started from the 2<sup>nd</sup> ~ 4<sup>th</sup> day (28 cases, 70%), and with the starting dose of 2.4 ± 0.9 mg. For bridging group, warfarin was started from the 2<sup>nd</sup> ~ 5<sup>th</sup> day (52 cases, 89.6%), and the remaining 6 cases (10.4%) was started from the 5<sup>th</sup> day after surgery, with the dose of 3.0 ± 0.8 mg. Shown in **Table 2** are the perioperative INR, bleeding complications, and length of hospital stay of the three groups. As to hematoma incidence, there was no difference (P = 0.125) in the three groups. Only one patient in the continued group was on aspirin and warfarin combined at the time of device implantation, but no bleeding events occurred which was shown in **Table 2**. No perioperative thromboembolic event was observed in these groups.

### **Discussion**

Although guidelines suggest that patients after mechanical heart valve replacement with long-term warfarin anticoagulation who undergo device implantation use therapeutic doses of low molecular weight heparin subcutaneously or intravenous heparin as bridging treatment, some clinical studies have shown that bridging therapy comes with a high risk of bleeding. Wiegand [2] et al performed a retrospective analysis on pouch hematoma in 3124 cases of pacemaker implantation patients, in which 1069 required oral anticoagulation therapy. Treatment with phenprocoumon was discontinued 1 to 5 days before implantation and was replaced by high-dose heparinization as bridging anticoagulant therapy according to the thromboembolic risk of the patients. The results show that compared with patients on persistent use of warfarin the therapeutic dose bridging therapy substantially increased the hematoma rate (10.7% vs. 2.9%, respectively; p <0.001) without reducing the rate of arterial embolism within the first month after implantation (0.18% vs. 0.21%, respectively; difference is not significant).

Given the higher incidence of hemorrhagic events associated with heparin bridging, physicians currently tend to perform implantation without reversal of warfarin. More and more evidence shows that little or no increased risk of bleeding occurred in the continued warfarin therapy in the procedure of device implantation. Thal's [3] study enrolled 200 cases of patients taking antiplatelet drugs and/or warfarin. In the study, a total of seven patients (3.5%) were identified with a complicating hematoma in the periprocedural time window. Three of these seven patients were taking warfarin at the time of device implantation, which was not different compared with the group on no anticoagulation (P = 0.67). An interesting finding from

our study is that five of the seven hematomas (71%) occurred in patients on DAPT, which is different ( $P = 0.0001$ ) compared with the patients without DAPT. Tompkins [4] studied 1388 patients and the results showed that dual antiplatelet therapy and heparin are the risk factors of bleeding, while for the patients who continued warfarin therapy with  $INR \geq 1.5$  ( $n = 46$ ), there was no difference in bleeding events (6.5% vs. 4.3%,  $P = 0.50$ ) compared to the discontinued group ( $n = 258$ ). A new study [5] compared continued warfarin anticoagulation group ( $n = 129$ ) with previous bridging group in high-risk patients ( $n = 62$ ), and the results showed that continued warfarin therapy can significantly reduce the incidence of hematoma (2.3% vs. 17.7%,  $P = 0.0001$ ).

In this study, we retrospectively reviewed consecutive patients underwent permanent pacemaker implantation with long-term warfarin therapy after valve replacement in our hospital. The results showed that there was no significant difference ( $P = 0.125$ ) in hematoma rate among continued group, discontinued group, and bridging group, but there was much more wound dehiscence in the bridging group. The INR value in continued group was significantly higher than the bridging group and the discontinued group during surgery, but the bleeding complications were less than that in bridging group. Discontinued group showed an advantage in reducing wound dehiscence. The study shows that if warfarin is continued, it will not increase the risk of bleeding when the International Normalized Ratio (INR) is around 1.7 during the procedure. In this study, there was no arterial thromboembolic event occurred in the discontinued group. Small as the sample of our study is, it cannot suggest the safety of discontinued warfarin. There is no doubt that discontinued warfarin makes patients exposure to the risk of thromboembolic event, and large and even multicentre studies are needed to perform to get a definitive answer for the management of these patients.

Some similar studies also indicated the advantage of continued warfarin therapy in these patients, especially in patients with moderate to severe thromboembolic risk. Tischenko [6] et al enrolled 1562 cases of patients undergone pacemaker implantation (447 cases were on long-term warfarin therapy) consecutively. Group 1 consisted of 117 consecutive patients

on long-term warfarin therapy with significant risk of thromboembolism (atrial fibrillation with CHADS (2) score  $\geq 2$ , mechanical heart valve, recent venous thromboembolism) who underwent arrhythmia device implantation without interruption of warfarin. Group 2 was 117 patients who served as age- and sex-matched controls matched to procedure type not taking warfarin. Group 3 consisted of 38 similar thromboembolic risk historical control patients who underwent interruption of warfarin therapy and bridging with dalteparin before and 24 hours after surgery. The results showed that the mean international normalized ratio in group 1 patients was  $2.2 \pm 0.4$  (age 79  $\pm$  11 years, 73 male). Significant hematoma was noted in 9 patients (7.7%). Five group 2 patients (control) had significant hematomas (4.3%). In group 3, 9 patients developed significant hematomas (23.7%,  $P = .012$ ). This result indicated that although the INR in continued group is around 2.2, the hematoma rate of the group is lower than the bridging group. Ahmed [7] et al analyzed 459 patients on chronic warfarin therapy who underwent device surgery retrospectively. Warfarin was continued in 222 patients during the perioperative period, and it was temporarily held and bridging therapy administered in 123 patients and was temporarily held without bridging therapy in 114 patients. Patients who continued taking warfarin had a lower incidence of pocket hematoma ( $P = .004$ ) and a shorter hospital stay ( $P < .0001$ ) than patients in the bridging group did. Holding warfarin without bridging is associated with a higher incidence of transient ischemic attacks ( $P = .01$ ).

The safety of continued warfarin anticoagulation lies in that: the devices are usually implanted above pectoral fascia with fewer blood vessels. The better the hemostasis is done, the less dehiscence would happen. At the same time, continued warfarin therapy avoided the application of heparin which can increase the length of hospital stay and the incidence of bleeding complications.

Although some small scale, randomized and controlled studies supported that it is safe and effective to perform heart device implantation in patients with continued warfarin therapy, most of the studies are retrospective. Larger samples of randomized, double-blinded, and controlled studies are still needed to confirm whether continued warfarin therapy on individ-

uals of different risk levels is the best anticoagulation strategy.

### Acknowledgement

This study is funded by High Level Health Technical Personnel Training Plan (2009-3-48) of Beijing Health Bureau. The paper has not been submitted elsewhere. All the authorships are aware of and approve the manuscript being submitted to this journal.

**Address correspondence to:** Xue-Jun Ren, Department of cardiology, Institute of Heart Lung and Blood Vessel Disease, Beijing Anzhen Hospital Affiliated to Capital Medical University, Beijing 100029, China. Phone: +861064456901; Fax: +861064456503; E-mail: renxj@163.com

### References

- [1] Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, Ansell J; American College of Chest Physicians. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133: 299S.
- [2] Wiegand UK, LeJeune D, Boguschewski F, Bonnemeier H, Eberhardt F, Schunkert H, Bode F. Pocket hematoma after pacemaker or implantable cardioverter defibrillator surgery: influence of patient morbidity, operation strategy, and perioperative antiplatelet/anticoagulation therapy. *Chest* 2004; 126: 1177.
- [3] Thal S, Moukabary T, Boyella R, Shanmugasundaram M, Pierce MK, Thai H, Goldman S. The relationship between warfarin, aspirin, and clopidogrel continuation in the peri-procedural period and the incidence of hematoma formation after pacemaker implantation. *Pacing Clin Electrophysiol* 2010; 33: 385.
- [4] Tompkins C, Cheng A, Dalal D, Brinker JA, Leng CT, Marine JE, Nazarian S, Spragg DD, Sinha S, Halperin H, Tomaselli GF, Berger RD, Calkins H, Henrikson CA. Dual antiplatelet therapy and heparin “bridging” significantly increase the risk of bleeding complications after pacemaker or implantable cardioverter-defibrillator pacemaker implantation. *J Am Coll Cardiol* 2010; 55: 2376.
- [5] Cano O, Muñoz B, Tejada D, Osca J, Sancho-Tello MJ, Olagüe J, Castro JE, Salvador A. Evaluation of a new standardized protocol for the perioperative management of chronically anticoagulated patients receiving implantable cardiac arrhythmia devices. *Heart Rhythm* 2012; 9: 361.
- [6] Tischenko A, Gula LJ, Yee R, Klein GJ, Skanes AC, Krahn AD. Implantation of cardiac rhythm devices without interruption of oral anticoagulation compared with perioperative bridging with low-molecular weight heparin. *Am Heart J* 2009; 158: 252.
- [7] Ahmed I, Gertner E, Nelson WB, House CM, Dahiya R, Anderson CP, Benditt DG, Zhu DW. Continuing warfarin therapy is superior interrupting warfarin with or without bridging anticoagulation therapy in patients undergoing pacemaker and defibrillator implantation. *Heart Rhythm* 2010; 7: 745.