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# Is Long-term Warfarin Therapy Necessary in Chinese Patients with Atrial Fibrillation after Bioprosthetic Mitral Valve Replacement and Left Atrial Appendage Obliteration?

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## ABSTRACT

**Background:** Long-term warfarin therapy has been used to decrease thromboembolic events in patients with atrial fibrillation (AF) following bioprosthetic mitral valve replacement (BMVR) and left atrial appendage obliteration (LAAO). A retrospective study was conducted to investigate the efficacy of long-term warfarin or aspirin therapy in patients with AF after BMVR and LAAO.

**Methods:** A total of 215 patients with persistent AF were given anticoagulation therapy with warfarin for the first 3 months after BMVR and LAAO, continuing warfarin or aspirin therapy according to the surgeon's preference. A yearly follow-up with patients was performed by telephone or mail for postoperative condition, cerebrovascular, and bleeding events.

**Results:** Seven patients died in the first 3 months after surgery, including 6 patients from heart failure and 1 patient from sudden death. The remaining 208 patients were divided into two groups: warfarin group (n = 84 patients) and aspirin group (n = 124). The patients in the warfarin group were older than those in the aspirin group and had a lower postoperative left ventricular ejection fraction. Other baseline and operative characteristics were similar. The two groups had similar incidence of thromboembolic events (9.5% versus 8.9%, $P$ = .873) and bleeding events 7.1% versus 3.2%, $P$ = .207). Each group had one intracranial hemorrhage. Eleven patients expired within three months after surgery, 4 4.8%) in the warfarin group and 10 8.1% in the aspirin group ($P$ = .411 by Fisher exact test). Cumulative survival was not significantly different in the two groups by Kaplan-Meier analysis ($P$ = .55, log-rank test).

**Conclusion:** At the current time in China, long-term warfarin or aspirin therapy may have no significantly different impact on long-term prognosis after 3 months anticoagulation with warfarin in patients with AF undergoing BMVR and LAAO.

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## INTRODUCTION

Mitral valvular heart disease often combines with atrial fibrillation (AF). Thromboembolism is a major complication after bioprosthetic mitral valve replacement (BMVR) in patients with AF. The most recent guidelines published by the leading societies of cardiothoracic surgery in Europe and the United States recommended long-term use of aspirin following anticoagulation therapy with a vitamin K antagonist (VKA) for the first three months after BMVR for patients in sinus rhythm, and recommended lifelong anticoagulation for patients with bioprostheses who have atrial fibrillation [Taylor 2012; Nishimura 2014]. Currently, left atrial appendage obliteration (LAAO) is routinely performed during BMVR operation [Kim 2013], which is also performed to reduce thromboembolism in patients with lone AF [Meincke 2013]. Most Chinese patients do not continue warfarin therapy and switch to aspirin because of adverse effect of warfarin and inconvenience of monitoring the level of international normalized ratio (INR) [Zuo 2010]. There are no studies examining the long-term effect of antiplatelet agents in patients with BMVR. The beneficial effects seen with bioprosthetic aortic valves were presumed to apply to mitral valves [Nishimura 2014]. The aim of the present retrospective study was to analyze whether long-term warfarin or aspirin therapy resulted in differences in outcomes of patients with AF after BMVR and LAAO following three-month anticoagulation.

## MATERIALS AND METHODS

The present study was based on the consecutive experience of our institution (the Chinese PLA General Hospital, Beijing, China) regarding outcomes of patients with persistent AF undergoing BMVR and LAAO, who survived 3 months after surgery.

Baseline characteristics and comorbidity were recorded by a patient's personal physician at our institution. Preoperative echocardiographic data were prospectively measured for patient evaluation and collected for this study by electronic download without alteration.

Study subjects inclusion criteria were as follows: 1) Persistent AF; and 2) BMVR and LAAO at our institution between October 1, 2002, and October 31, 2014. Exclusion criteria were the presence of simultaneous tricuspid valve replacement (tricuspid repair was not an exclusion criteria). Patients

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with associated coronary artery bypass grafting (CABG) and bioprosthetic aortic valve replacement were not excluded.

Medtronic Hancock porcine prosthesis, St. Jude Medical porcine prosthesis, and Carpentier-Edwards pericardial prosthesis were utilized. Bioprosthesis use was based on discussion between patient and surgeon. All operations were performed by senior attending surgeons. Standard, well-validated bioprosthetic mitral valve replacement techniques were used to insure valvular competence, including leaflet resection and chordal preservation as best as was possible. LAAO technique was performed at each surgeon's discretion and varied, including two layer running endocardial suture and left atrial appendage ligation, most of which was running endocardial suture in our institution.

Postoperatively, warfarin was started on postoperative day 1 or 2 in all stable non-bleeding patients after extubation. Warfarin was used for the first three months postoperatively with a target INR of 1.8-2.5 as recommended [Camm 2010], and the INR was tested monthly. Thereafter, warfarin was continued or aspirin was given according to the attending surgeon. Intravenous heparin was used as a bridge to therapeutic postoperative anticoagulation. Patients who underwent a concomitant CABG were usually given aspirin or clopidogrel in addition to warfarin. However, dual antiplatelet drug therapy was usually not utilized due to an increased risk of hemorrhagic complications. The patient status, NYHA class, cerebrovascular events, and bleeding events were followed up on yearly by telephone calls or mail to patients and families.

### *Statistical Analysis*

Continuous variables were expressed as a mean ± standard deviation. Student *t* test and Pearson $x^2$ test or Fisher exact test were used to analyze continuous and categorical variables respectively. A time-censored Kaplan-Meier cumulative analysis was performed to assess the survival rate between the aspirin group and the warfarin group. All P values were two sided, and a value of $P < .05$ was regarded as statistically significant. SPSS 19.0 (IBM, Armonk, NY, USA) was used for statistical analysis.

## RESULTS

### *Patients*

A total of 215 patients (100 female; 115 male) had a mean age of 66.3 ± 5.38 years. Mitral valve disease etiology was mitral valve degeneration or mitral valve leaflet prolapse in 67 patients, rheumatic heart valve disease in 139 patients, ischemic heart disease in 5 patients, infectious endocarditis in 2 patients, and mechanical perivalvular leak in 2 patients. Patients undergoing concomitant cardiac surgical procedures included: 32 CABG, 28 bioprosthetic aortic valve replacement, and 145 tricuspid repair. Median time of follow-up was 50 months (quantile: 31-60). Seven patients died within 3 months after surgery, 6 patients from heart failure and 1 patient from sudden death. These patients were not included in the analysis, as anticoagulation therapy within 3 months was the same in all patients. The remaining 208 patients were divided into two groups according to long-term use of warfarin or aspirin: warfarin group (n = 84) and aspirin group (n = 124). The patients'preoperative characteristics are listed in Table 1. The patients in the warfarin group were older than the patients in the aspirin group. Other baseline patient characteristics were similar between the groups including cardiac function, baseline echocardiographic data, renal function, CHADS2 mean score, and history of cerebral infarction.

Table 1. Baseline Patient Characteristics

| Variable | Warfarin Group (n = 84) | Aspirin Group (n = 124) | *P* |
|---|---|---|---|
| Age, y | 65.2 ± 4.3 | 66.8 ± 5.9 | .026 |
| Female sex, n (%) | 28 (54.9) | 34 (55.7) | .929 |
| Hypertension, n (%) | 11 (13.1) | 28 (22.6) | .085 |
| Diabetes, n (%) | 5 (6.0) | 11 (8.9) | .329 |
| Prior cerebral infarction, n (%) | 11 (13.1) | 15 (12.1) | .831 |
| NYHA classification, n (%) | 2.88 ± 0.547 | 3.00 ± 0.612 | .152 |
| CHADS2 mean scores | 0.54 ± 0.884 | 0.52 ± 0.801 | .922 |
| Renal failure, n (%) | 1 | 1 | NS |
| Last creatinine level, mmol/L | 79.2 ± 20.3 | 84.8 ± 22.2 | .0662 |
| Left atrial dimension, mm | 56.0 ± 11.0 | 54.0 ± 12.0 | .212 |
| LVEDD, mm | 47.6 ± 8.9 | 48.4 ± 8.0 | .553 |
| LVEF, % | 59.8 ± 9.3 | 61.6 ± 10.4 | .208 |

NYHA indicates New York Heart Association; LAD, left atrial dimension; LVEDD, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; NS, not significant.

Table 2. Operative Patient Characteristics for the Two Groups

| Variable | Warfarin Group (n = 84) | Aspirin Group (n = 124) | *P* |
|---|---|---|---|
| CPBT, min | 107.1 ± 35.9 | 110.5 ± 42.3 | .543 |
| ACT, min | 73.8 ± 28.9 | 74.2 ± 31.2 | .783 |
| Valve implant size, mm | 27.2 ± 1.5 | 26.6 ± 1.3 | .167 |
| Concomitant CABG, n (%) | 10 (11.8) | 5 (8.2) | .527 |
| Concomitant AVR, n (%) | 7 (13.7) | 8 (13.1) | .925 |
| Concomitant tricuspid valve repair, n (%) | 38 (74.5) | 44 (72.1) | .777 |
| Left atrial thrombus removal, n (%) | 17 (33.3%) | 13 (21.3) | .153 |
| Intraoperative IABP placement, n (%) | 1 (1.2) | 2 (1.6) | NS |

CPBT indicates cardiopulmonary bypass time; ACT, aortic cross-clamp time; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; IABP, intra-aortic balloon pump; NS, not significant.

The operative characteristics of both groups are listed in Table 2. There were no significant differences in cardiopulmonary bypass time, aortic cross-clamp time, and valve implant size. Concomitant procedures were similar in both groups including bioprosthetic aortic valve replacement, tricuspid valve repair, CABG, intraoperative intra-aortic balloon pump (IABP) placement, and left atrial thrombus removal.

### *Short-term Outcomes*

Table 3 shows short-term outcomes of patients for the first 3 months after surgery. Three patients (3.6%) had cerebral infarction or transient ischemic attack (TIA) in the warfarin group and 2 (1.6%) in the aspirin group ($P$ = .395). One patient in the aspirin group had gastrointestinal bleeding events, and received warfarin therapy plus aspirin. Eleven patients (13.1%) had pleural effusions in the warfarin group and 15 patients (11.3%) in the aspirin group ($P$ = .694). Postoperative echocardiographic data of the patients were similar in the two groups.

### *Long-term Outcomes*

Table 4 shows the long-term outcome of the patients after 3 months, which were similar in the two groups. Eight patients (8.6%) had thromboembolic events in the warfarin

Table 3. Characteristics of Postoperative Echocardiogram and Short-term Patient Outcome for the Two Groups before Discharge

| Variable | Warfarin Group (n = 84) | Aspirin Group (n = 124) | *P* |
|---|---|---|---|
| Cerebral infarction or TIA, n (%) | 3 (3.6) | 2 (1.6) | .395 |
| Intracranial hemorrhages, n (%) | 0 | 0 | NS |
| Gastrointestinal bleeding events, n (%) | 0 | 1 | NS |
| MI, n (%) | 0 | 0 | NS |
| Pleural effusions, n (%) | 11 (13.1) | 15 (11.3) | .694 |
| Mediastinal bleeding needing reoperation, n (%) | 0 | 1 | NS |
| mediastinitis, n (%) | 0 | 0 | NS |
| New renal failure requiring dialysis, n (%) | 0 | 0 | NS |
| Heart block requiring permanent pacemaker, n (%) | 0 | 0 | NS |
| Postoperative ventilator, h | 19.2 ± 10.3 | 18.8 ± 9.2 | .77 |
| pLAD, mm | 46.1 ± 9.0 | 47.1 ± 11.1 | .577 |
| pLVEDD, mm | 43.3 ± 8.8 | 44.5 ± 5.2 | .405 |
| pLVEF, % | 56.7 ± 7.8 | 59.3 ± 8.5 | .03 |
| Mitral valve gradient, mmHg | 12.3 ± 4.2 | 12.8 ± 4.3 | .631 |

TIA indicates transient ischemic attack; MI, myocardial infarction; LAD, left atrial dimension; LVEDD, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; p, postoperative; NS, not significant.

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Table 4. Long-term Patient Outcomes

| Variable | Warfarin Group (n = 84) | Aspirin Group (n = 124) | *P* |
|---|---|---|---|
| Thromboembolic events, n (%) | 8 (9.5) | 11 (8.9) | .873 |
| Stroke, n (%) | 3 (3.6) | 6 (4.8) | .442 |
| TIA, n (%) | 5 (5) | 4 (3.2) | |
| Peripheral-artery embolic events, n (%) | 0 | 1 | NS |
| Bleeding events, n (%) | 6 (7.1) | 4 (3.2) | .207 |
| Intracranial hemorrhages, n (%) | 1 (1.2) | 1 (0.81) | NS |
| Deaths | 4 (4.8) | 10 (8.1) | .411 |

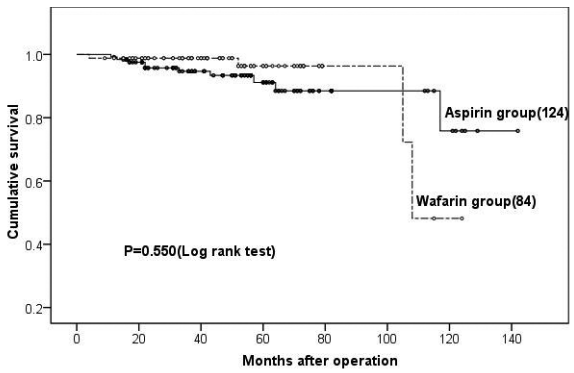
TIA indicates transient ischemic attack; NS, not significant.

group and 11 (8.9%) in the aspirin group (*P* = .442). One patient in the aspirin group had a peripheral embolism event. Two patients had intracranial hemorrhage events (one in each group). Bleeding events in all were 6 (7.1%) in the warfarin group and 4 (3.2%) in the aspirin group (*P* = .207). Fourteen (6.73%) of 208 patients died during the follow-up: 4 (4.8%) in the warfarin group and 10 (8.1%) in the aspirin group, (*P* = .411). Cumulative survival rate was not significantly different in the two groups by Kaplan-Meier analysis (*P* = .952, log-rank test) (Figure).

## DISCUSSION

As far as we know, this is the first study in China that evaluated long-term warfarin or aspirin therapy on long-term outcomes of patients with AF after BMVR and LAAO. The results showed that long-term warfarin or aspirin therapy may have no significantly different impact on long-term prognosis and survival of patients with AF after BMVR and LAAO with a three-month warfarin therapy.

As thrombosis most likely occurs within 3 months after tissue valve implantation [Edmunds 1987], the current guidelines recommend 3 months of anticoagulation after surgery whether the patients have high risk factors or not. After 3 months, the tissue valve can be treated like native valve disease, and VKA can be discontinued in more than two thirds of patients with tissue valves. In the remaining patients with associated risk factors for thromboembolism such as AF, previous thromboembolism, or hypercoagulable condition, lifelong VKA therapy is indicated [Nishimura 2014]. In the present study, the main risk factor of thromboembolism was AF.




Kaplan-Meier analysis of long-term cumulative survival with long-term warfarin or aspirin therapy (log rank test).

The target INR in the study was 1.8-2.5, which was consistent with the majority of Chinese literature [Ma 2012]. A Japanese guideline about AF recommended anticoagulation treatment with a target INR of 1.6-2.6 [Guidelines for Pharmacotherapy of AF 2010], which can achieve effective anticoagulation without increasing bleeding complications. We did not observe higher incidence of systemic embolism than that reported in the previous study [Suzuki 2007]. We used CHADS2 score to evaluate the risk for patients in the study, which was similar in both groups. CHA2DS2-VASC score is based on the data of European patients, while stroke type of Asian patients is different to that of European patients, so it is not clear whether CHA2DS2-VASC score is suitable for Chinese patients with AF.

Currently, LAAO is routinely performed in patients undergoing mitral valve replacement (MVR) with the aim of reducing the risk of thromboembolic events, which was recommended in recent guidelines (Class IIb) [Nishimura 2014]. But no RCTs have demonstrated a beneficial impact [Kim 2013]. The cause of BMVR was mitral stenosis or mitral regurgitation. When mitral stenosis is combined with AF, mitral stenosis increased the incidence of thrombosis in patients with AF [Atak 2004], while the secondary mitral regurgitation reduced the possibility of left atrial thrombosis [Fukuda 2011]. BMVR or MVR significantly decreased the incidence of left atrial thrombosis in patients with mitral stenosis, while patients with mitral regurgitation lost the protective effect after BMVR or mitral valve repair. But the simultaneous implementation of LAAO significantly reduced the chance of left atrial thrombosis [Emmert 2014; Lewalter 2013] because the left atrial appendage is recognized as a prime nidus of thrombus formation in patients with AF, and indeed the leading source of cardiogenic stroke. The recommendation from the previous guidelines is based on the

results of a study from Turpie et al [Turpie 1993]. Ten years ago, left atrial appendage obliteration procedure was not routinely performed worldwide and the previous reports had not considered the effect of LAAO on thromboembolic complication in patients with AF.

Antithrombotic therapy is controversial for patients with AF and bioprosthetic valves. Various guidelines [Taylor 2012; Nishimura 2014] recommend a three-month administration of warfarin therapy for patients in sinus rhythm after bioprosthetic valve replacement, following long-term use of aspirin; and long-term use of warfarin for patients with AF. Evidence supporting this recommendation is based on bioprosthetic aortic valve replacement [Taylor 2012; Colli 2013]. American guidelines for the management of patients with AF in 2014 recommended anticoagulation for patients with a mechanical valve, but did not refer patients with bioprosthetic valves [January 2014]. 2014 American guidelines for valvular heart disease only recommended that patients with bioprosthetic mitral valve in sinus rhythm should receive warfarin therapy for the first 3 months (Class IIa: LOE C), following long-term use of aspirin 75-100 mg (Class IIa: LOE B) based on evidence of aortic bioprostheses [Nishimura 2014]. 2010 ESC guidelines recommended lifelong anticoagulation for patients with AF after bioprosthetic valve replacement (Class IIa: LOE C), but without evidence to support this [Camm 2010].

Regardless of whether patients take warfarin, a recent randomized prospective epidemiologic study included 497 patients with AF and mitral stenosis or mitral valve replacement, and showed that only 83.1% of the patients currently took warfarin, of which only 36.1% achieved anticoagulation target level, while 19.1% of patients' INR was unstable. Multivariate analysis showed that only age was an independent predictor of thromboembolic events [Kaya 2014]. For patients in sinus rhythm, a retrospective study [Colli 2010] showed that no specific antithrombotic therapy modality was superior for patients undergoing BMVR. ANSWER study [Brennan 2012] enrolled patients undergoing BMVR, and patients with AF were included. The results showed that during follow-up, patients treated with warfarin had similar incidence of embolic events, but a substantially higher incidence of bleeding than those not treated with warfarin during their 3 months follow-up, based on the patients' INR and length of time within the therapeutic range. Patients were much more likely to have a bleeding event when their maximum INR was >3.0 compared to those whose maximum INR was 3.0 or less (16% versus 3%). Similarly, patients who spent no time with an INR over 3.0 were much less likely to have a bleeding event than those who spent more than 30% of the time with such an elevated INR (3% versus 26%). The present study did not report patients' INR, but results from ANSWER have indicated that the higher the INR, the greater the risk of bleeding. ACTION registry study showed that compared with aspirin, treatment with warfarin was associated with higher morbidity within 6 months after bioprosthetic AVR; particularly after concomitant CABG surgery, recipients of bioprosthetic AVR should receive prophylactic aspirin instead of warfarin [Colli 2013].

***Conclusion***

Currently, Chinese patients with AF should receive 3 months of warfarin therapy after BMVR and LAAO, thereafter long-term warfarin or antiplatelet therapy may have no significant difference on the thromboembolism or survival. Taking into account the instability of warfarin and potential bleeding complications, aspirin use may be recommended for these patients, but this is based on the results of a retrospective study of limited sample size. Therefore, further randomized controlled trials with large sample size may provide more evidence to support our proposal.

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