D-Dimer to Predict the Clinical Outcomes in Patients with Mechanical Heart Valve Replacement During Oral Anticoagulation Therapy

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Summary

Mechanical heart valve replacement (MHVR) entails lifetime oral anticoagulation to eliminate thrombosis. However, adverse events may still occur despite proper anticoagulation therapy. In this study, we investigated whether D-dimer can predict the clinical events in post-MHVR patients during oral anticoagulation therapy.

This was a single-center, prospective study. In all, 772 patients who underwent MHVR in the Wuhan Asia Heart Hospital from January 2013 to May 2014 were screened. Patients were assigned to the abnormal D-dimer group and the normal D-dimer group according to the D-dimer levels measured 3 months after the beginning of the oral anticoagulation therapy regime. All patients were followed up for 24 months or until the observation of the endpoints, which included thrombotic events, bleeding events, and all-cause deaths.

A total of 718 patients were included in the analysis: 91 had abnormal D-dimer levels, and 627 had normal D-dimer levels. In all, 53 events were observed during 24 months. Compared with the normal D-dimer group, patients with abnormal D-dimer levels had a higher incidence of thrombotic events (10 versus 14; hazard ratio (HR): 5.36; 95% confidence interval (CI): 2.38-12.1; \( P < 0.001 \)), all-cause mortality (8 versus 13; HR: 4.65; 95% CI: 1.93-11.2; \( P < 0.001 \)), and a higher incidence of total events (16 versus 37; HR: 3.26; 95% CI: 1.81-5.86; \( P < 0.001 \)). No significant difference was observed in bleeding events (2 versus 21; HR: 0.72; 95% CI: 0.17-3.07; \( P = 0.66 \)).

D-dimer may be a useful marker to predict thrombotic events and all-cause deaths in post-MHVR patients during oral anticoagulation therapy (ClinicalTrials.gov; NCT01996657).

Key words: INR, Vitamin K antagonists, Warfarin, Thrombotic event, Bleeding

Mechanical heart valve replacement (MHVR) entails lifetime oral anticoagulation to mitigate thromboembolism. Vitamin K antagonists (VKAs) remain the only oral anticoagulants of choice for post-MHVR patients, and anticoagulation therapy is usually monitored using the international normalized ratio (INR) derived from the prothrombin time. However, thrombotic events and bleeding events still occur, even though INR is in a stable state. Hence, markers complementary to INR are necessary to overcome the inadequacy of using INR alone.

D-dimer, a product of cross-linked fibrin degradation, is only produced when both the blood coagulation and fibrinolytic pathways are concomitantly activated. Elevated D-dimer levels are highly correlated with adverse clinical outcomes, including thrombotic or cardiovascular events and other severe conditions, which cover most complications during oral anticoagulation therapy. Previous studies reported that D-dimer exhibited a good prognostic value in patients with atrial fibrillation (AF) or cancer. However, the prognostic value of D-dimer in post-MHVR patients during oral anticoagulation therapy has not been thoroughly elucidated to date.

In view of the aforementioned findings, we conducted a prospective study to assess whether D-dimer could predict the clinical outcomes in patients after MHVR during oral anticoagulation therapy.

Methods

Patient population: Patients eligible for this study were those with post-MHVR receiving warfarin anticoagulation therapy. In all, 772 patients receiving mitral valve replacement (MVR) or double valve replacement (DVR; me-
Mechanical heart valves in both the aortic and mitral position) were screened in the Wuhan Asia Heart Hospital from January 2013 to May 2014. We excluded patients who had recent (within 3 months) thrombosis or cerebral hemorrhage, those who had difficulty from the standpoint of compliance, or those who declined to participate. Ethical approval for this study was obtained from the Wuhan Asia Heart Hospital ethical committee (2013-P-002). All enrolled patients provided written informed consent. The protocol was also registered at the registry of clinical trials (ClinicalTrials.gov; NCT01996657) before commencement.

Laboratory assay: The D-dimer baseline was set up at 3 months on initiation of warfarin therapy. INR was used to monitor anticoagulation therapy and was measured once a month and during follow-up. INR and D-dimer were analyzed on an automatic analyzer (ACL-TOP 700, Instrumentation Laboratory, Bedford, MA). Specifically, INR was measured using HemosIL® RecombiPlasTin2G (international sensitive index: 0.98-1.01; Instrumentation Laboratory, Bedford, MA). Quality control was maintained using a commercial product (Lyphochek®, Bio-rad, Hercules, CA). The inter- and intraday variability coefficients were 1.89% and 2.15%, respectively. The D-dimer levels were determined by utilizing a latex-enhanced photometric immunoassay (HemosIL® D-dimer HS 500, Instrumentation Laboratory, Bedford, MA). Quality control was performed using an internal laboratory standard in-house plasma pool. The inter- and intraday variability coefficients were 3.36% and 4.57%, respectively. The D-dimer result was expressed in terms of fibrinogen units (μg/L). All measurements were performed at an onsite laboratory within 2 hours after blood sampling. A uniform cut-off value (500 μg/L) was used for D-dimer in patients under 50 years. An age-adjusted cut-off value was used for D-dimer in patients 50 years or older (age-adjusted cut-off = (age, years) × 10 μg/L).

Follow-up and endpoints: All patients were followed up for 24 months unless the endpoint events occurred. The endpoints were defined according to the associated guidelines, including thrombotic events, major bleeding events, and all-cause deaths. Specifically, thrombotic events included valve thrombosis, transient ischemic attack, ischemic stroke, peripheral embolism, and myocardial infarction. Major bleeding events included intracranial and retroperitoneal hemorrhage or a decrease in hemoglobin of at least 20 g/L or cases requiring the transfusion of 2 or more units of whole blood or red cells.

Statistical analysis: Continuous variables were expressed as the mean ± standard deviation. Categorical variables were presented as absolute numbers or percentages. The differences between groups were assessed by a t-test or a Mann-Whitney test analysis for continuous variables and by a chi-square test for categorical variables. Clinical events were shown by Kaplan-Meier event-free curves and compared using log-rank tests. The hazard ratio (HR) and 95% confidence interval (CI) were calculated by the Cox proportional-hazards model. A P value < 0.05 was considered to be statistically significant. The data were analyzed by Medcalc version 16.2.1 (Medcalc Statistical Software, Ostend, Belgium) and GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA).

Results

Participants and exclusions: The enrolment and a flow chart of the study are shown in Figure 1. A total of 772 patients were initially screened at Wuhan Asia Heart Hospital before the study. After excluding 33 patients who were not able to fully participate in the study, 739 patients were enrolled. Next, 14 patients were removed from the study: 7 failed to reach the target INR (the mean INR was out of target range), and 7 were lost to follow-up. Overall, 718 patients completed the study and were included in the analysis.

Baseline characteristics: Table I lists the basic clinical characteristics of the patients, including age and gender, valve position, diabetes, hypertension, and other related medical information. A total of 91 patients with abnormal D-dimer (AD group) and 627 patients with normal D-dimer (ND group) levels were included in the analysis. Significant differences were seen in age, diabetes mellitus, stroke history, AF, New York Heart Association (NYHA) ≥ III, D-dimer levels, and average INR levels between the 2 groups.

Incidence of clinical outcome: All the events are listed in Table II. In all, 53 events were observed during the follow-up. Of the 24 patients who experienced thrombotic
events, 10 had abnormal D-dimer levels. Of the 23 patients who experienced bleeding events, 2 had abnormal D-dimer levels. Of the 21 all-cause deaths, 8 patients had abnormal D-dimer levels, 4 died from thrombotic events, 11 died from bleeding events, and the remaining 6 died from heart failure and other noncardiac causes. Compared with the ND group, the AD group had a substantially higher incidence of thrombotic events (HR: 4.36; 95% CI: 2.29-12.1; P < 0.001; Figure 2A), however, there was no significant difference in the incidence of bleeding events between the 2 groups (HR: 0.72; 95% CI: 0.17-3.07; P = 0.66; Figure 2B). Besides, the AD group also had a significantly higher all-cause mortality (HR: 4.65; 95% CI: 1.93-11.2; P < 0.001; Figure 2C), and incidence of total events (HR: 3.26; 95% CI: 1.81-5.86; P < 0.001; Figure 2D).

**Prognostic values of D-dimer:** The Cox proportional-hazards model analysis listed in Table III showed that D-dimer was independently correlated with thrombotic events (HR: 5.32; 95% CI: 2.29-12.3; P < 0.001), all-cause deaths (HR: 3.55; 95% CI: 1.42-8.86; P < 0.001), and total events (HR: 2.54; 95% CI: 1.39-4.65; P < 0.001) after being adjusted by age, diabetes mellitus, stroke history, AF, NYHA ≥ III, and average INR levels.

**Discussion**

This prospective study was conducted to evaluate the prognostic value of D-dimer levels in patients with MHVR during oral anticoagulation therapy and provided evidence that patients with abnormal D-dimer levels experienced more thrombotic events and all-cause mortality than those with normal D-dimer levels.

Patients who underwent valve replacement required oral anticoagulant therapy because of the interaction of blood with the surface material of valve prostheses and nonphysiological blood flow. An appropriate intensity of anticoagulation should be achieved to reduce thromboembolic complications.

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**Table I.** Baseline Clinical Characteristics

|                      | All patients (n = 718) | Abnormal D-dimer (n = 91) | Normal D-dimer (n = 627) | P value |
|----------------------|------------------------|---------------------------|--------------------------|---------|
| Age, years           | 49.7 ± 11.4            | 52.0 ± 9.2                | 49.4 ± 11.6              | 0.016   |
| Age ≥ 50 years, n (%)| 343 (47.8)             | 50 (54.9)                 | 293 (46.7)               | 0.14    |
| Male, n (%)          | 313 (43.6)             | 39 (42.9)                 | 274 (43.7)               | 0.88    |
| Valve position       |                        |                           |                          |         |
| MVR, n (%)           | 502 (69.9)             | 60 (65.9)                 | 442 (70.5)               |         |
| DVR, n (%)           | 216 (30.1)             | 31 (34.1)                 | 185 (29.5)               |         |
| Diabetes mellitus, n (%)| 128 (17.8)            | 23 (25.3)                 | 105 (16.7)               | 0.047   |
| Hypertension, n (%)  | 208 (29.0)             | 27 (29.7)                 | 181 (28.9)               | 0.87    |
| Smoker, n (%)        | 249 (34.7)             | 33 (36.3)                 | 216 (34.4)               | 0.73    |
| Stroke history, n (%)| 44 (6.1)               | 10 (11.0)                 | 34 (5.4)                 | 0.039   |
| Atrial fibrillation, n (%)| 385 (53.6)         | 60 (65.9)                 | 325 (51.8)               | 0.012   |
| NYHA ≥ III, n (%)    | 67 (9.3)               | 15 (16.5)                 | 52 (8.3)                 | 0.012   |
| D-dimer, μg/L (IQR)  | 153 (82, 282)          | 782 (632, 1164)           | 134 (75, 214)            | <0.01   |
| INR*                 | 2.43 ± 0.41            | 2.50 ± 0.30               | 2.42 ± 0.42              | 0.038   |
| TTR, %               | 69.5 ± 10.6            | 68.0 ± 10.4               | 69.7 ± 10.6              | 0.17    |

MVR indicates mitral valve replacement; DVR, double valve replacement (mechanical heart valves in both the aortic and mitral position); NYHA, New York Heart Association; IQR, interquartile range; INR, international normalized ratio; and TTR, time in therapeutic range. *Average INR during follow-up.

**Table II.** Incidence of Main Outcomes

|                      | Total (n = 718) | Abnormal D-dimer (n = 91) | Normal D-dimer (n = 627) |
|----------------------|----------------|---------------------------|--------------------------|
| Thrombotic events, n (%)| 24 (3.3)      | 10 (11.0)                 | 14 (2.2)                 |
| Ischemic stroke, n (deaths) | 14 (2)       | 5 (1)                     | 9 (1)                    |
| Valve thrombosis, n (deaths) | 3 (2)        | 2 (1)                     | 1 (1)                    |
| Transient ischemic attack, n | 2            | 1                         | 1                        |
| Peripheral embolism, n | 2             | 2                         | 0                        |
| Myocardial infarction, n | 3             | 0                         | 3                        |
| Bleeding events, n (%) | 23 (3.2)      | 2 (2.2)                   | 21 (3.3)                 |
| Cerebral hemorrhage, n (deaths) | 15 (8)     | 1 (1)                     | 14 (7)                   |
| Gastrointestinal bleeding, n (deaths) | 7 (2)   | 1 (1)                     | 6 (1)                    |
| Hematuria, n (deaths) | 1 (1)         | 0                         | 1 (1)                    |
| All-cause deaths, n (%) | 21 (2.9)      | 8 (8.8)                   | 13 (2.1)                 |
| Death from thrombosis, n | 4             | 2                         | 2                        |
| Death from bleeding, n | 11            | 2                         | 9                        |
| Death from heart failure, n | 3            | 2                         | 1                        |
| Death from cancer, n | 1             | 1                         | 0                        |
| Unexplained death, n | 2             | 1                         | 1                        |
| Total events, n (%) | 53 (7.4)      | 16 (17.6)                 | 37 (5.9)                 |
bolism without increasing bleeding. Guidelines have recommended a standard intensity with a target INR of 2.5-3.5 for patients with MVR or DVR. However, the uniform target INR for Chinese patients is still under debate. Previous studies have suggested a low anticoagulation intensity with a target INR of 1.5-2.5 for Chinese patients post-MHVR, because the standard intensity may cause more bleeding in Chinese patients than in their Caucasian counterparts owing to the polymorphism of the hematic gene and differences in factor levels, endothelial markers, platelet reactivity, and thrombolytic status.

On the basis of the above findings, a target INR range of 1.8-3.5 was used in this study. The average INR was 2.43, which is lower than the standard intensity.

The D-dimer value in patients on VKA therapy in terms of prognosis assessment has been described in previous studies. Giansante, et al. reported a 2-year follow-up study in 132 patients after MHVR. In their observational study, patients with elevated D-dimer levels had a 5-fold higher risk of thrombotic events, which was consistent with our findings. Similarly, a number of studies demonstrated that AF patients with abnormal D-dimer levels during VKA therapy tended to have more thrombotic events and cardiovascular events as well. However, one difference was that part of these studies observed that abnormal D-dimer levels were associated with bleeding events.

Figure 2. Kaplan-Meier analysis for the cumulative incidence of events. Kaplan-Meier curves for the 2 groups. A: Comparison of the incidence of thrombotic events between the 2 groups. B: Comparison of the incidence of bleeding events between the 2 groups. C: Comparison of all-cause mortality between the 2 groups. D: Comparison of the incidences of total events between the 2 groups.

Table III. Abnormal D-Dimer Levels for Clinical Outcomes by Cox Proportional-Hazard Analysis

| Outcome                  | Unadjusted HR (95% CI) | P value | Adjusted HR* (95% CI) | P value |
|--------------------------|------------------------|---------|-----------------------|---------|
| Thrombotic events        | 5.36 (2.38-12.1)       | < 0.001 | 5.32 (2.29-12.3)      | < 0.001 |
| Bleeding events          | 0.72 (0.17-3.07)       | 0.66    | 0.54 (0.12-2.36)      | 0.41    |
| All-cause deaths         | 4.65 (1.93-11.2)       | < 0.001 | 3.55 (1.42-8.86)      | 0.007   |
| Total events             | 3.26 (1.81-5.86)       | < 0.001 | 2.54 (1.39-4.65)      | 0.003   |

HR indicates hazard ratio; and 95% CI, 95% confidence interval. *Adjusted by age, average INR during follow-up, and whether patients had diabetes mellitus, stroke history, atrial fibrillation, and NYHA ≥ III.
No significant correlation was found between D-dimer elevation and bleeding events in the current study, which might be because the D-dimer levels were only measured at the beginning of the study. The D-dimer level at the moment of bleeding events was unknown.

D-dimer elevation may be seen in several diseases or situations. Historically, a lack of specificity has been regarded as a disadvantage of D-dimer assessments; however, the low specificity has been transformed into an advantage in the evaluation of anticoagulation prognosis. In the current study, 3 patients died from heart failure, 1 patient died from cancer, and most of them (3/4) had abnormal D-dimer levels. Previous studies reported that D-dimer levels are able to predict deaths in patients with heart failure. A similar prognostic value was demonstrated in patients with cancer. Therefore, D-dimer has the potential to predict all-cause events.

There are several limitations to this study. First, the study may have selection bias because it is a single-center study, even if it has sufficient power to detect significant differences between the groups in the main outcomes. Despite our efforts to include all qualified patients, several patients refused to participate in the study because of certain constraints in revisiting our center, as required. Second, as mentioned above, the D-dimer level was only measured at 3 months after starting warfarin to avoid a stress-associated D-dimer elevation after surgery. In addition, there were differences in the stages in which a stable anticoagulation state had been achieved. We did not dynamically monitor D-dimer levels. Hence, we did not know whether the D-dimer levels that had been originally normal became abnormal during follow-up, and the D-dimer level at the time of the adverse events was unknown. Dynamic measurement of D-dimer levels might give more information.

Conclusions
D-dimer may be a useful and complementary marker to INR to predict thrombotic events and deaths in post-MHVR patients during oral anticoagulation therapy.

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Disclosure
Conflicts of interest: The authors report no relationships that could be construed as a conflict of interest.

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