Original Article

Effects of Medical Treatment on the Prognosis and Risk of Embolic Events in Patients with Severe Aortic Plaque

Masataka Nishiga1, Chisato Izumi1, Hayato Matsutani2, Sumiyo Hashiwada2, Shuichi Takahashi2, Yukiko Hayama1, Seiko Nakajima1, Jiro Sakamoto1, Koji Hanazawa1, Makoto Miyake1, Toshihiro Tamura1, Hirokazu Kondo1, Makoto Motooka1, Kazuaki Kaitani1 and Yoshihisa Nakagawa1

1Department of Cardiology, Tenri Hospital, Tenri, Japan
2Department of Clinical Pathology, Tenri Hospital, Tenri, Japan

Aim: The optimal treatment strategy for patients with aortic atheroma is not well established because data regarding medical treatment for such patients are lacking, especially with respect to the Japanese population. The purpose of this study was to clarify the effects of medical treatment on the risk of embolic events and mortality in patients with severe aortic plaque.

Methods: We retrospectively investigated 75 consecutive patients with severe aortic plaque detected on transesophageal echocardiography (TEE) between 1995 and 2005. The occurrence of embolic events and all-cause death in the period after TEE was assessed. The cumulative incidence of subsequent embolic events and death was evaluated in relation to specific medical treatments, including statins, antiplatelet drugs and warfarin.

Results: Embolic events occurred in 27 patients (36%) and death occurred in 37 patients (49%) during follow-up (5.6 ± 3.0 years). The patients who experienced embolic events had a significantly higher prevalence of previous embolic events, atrial fibrillation and hemodialysis than the patients who did not experience embolic events. Univariate and multivariate analyses showed that the use of statins and/or antiplatelet drugs was significantly associated with a low incidence of death but not with a low incidence of embolic events. On the other hand, warfarin exhibited neither beneficial nor harmful effects on the incidence of embolic events or death.

Conclusions: Statin and antiplatelet drugs have beneficial effects on the prognosis of patients with severe aortic plaque diagnosed on TEE.


Key words: Aortic plaque, Transesophageal echocardiography, Statin, Antiplatelet therapy, Warfarin

Introduction

The presence of severe aortic plaque on transesophageal echocardiography (TEE) (Fig. 1) is a high risk factor for stroke and peripheral embolism1-6. We previously reported the poor prognoses of patients with severe aortic plaque detected on TEE in the Japanese population7, 8. However, there is no optimal therapeutic regimen for this high-risk group9, 10, and no randomized trials have been completed. With respect to the Japanese population in particular, there are no reports regarding the impact of specific medical treatments on the prognosis of patients with severe aortic plaque.

The protective effects of statins, such as reductions in the risk of stroke in patients with severe aortic plaque, have been reported in several nonrandomized studies9, 11-14. According to guidelines10 published in the United States in 2010, statin treatment is a reasonable option for patients with aortic arch atheroma (Class IIa, Level of Evidence: C).

With regard to antiplatelet and anticoagulation agents, the benefits of these drugs are more controversial than those of statin therapy. It has been reported
that warfarin is harmful in patients with aortic atheroma due to the theoretical risk of plaque hemorrhage resulting in peripheral embolization\(^{15-18}\). On the other hand, various nonrandomized studies have suggested that warfarin is not harmful in patients with aortic atheroma and may in fact have potential benefits for preventing stroke\(^{19-22}\). The guidelines state that the use of oral antiplatelet or anticoagulation therapy may be considered in stroke patients with aortic arch atheroma (Class IIb, Level of Evidence: C)\(^{10}\).

Aim

The purpose of this study was to clarify the clinical characteristics of patients with severe atheromatous plaque in the thoracic aorta and the impact of specific medical therapies, including statins, antiplatelet drugs and warfarin, on the incidence of subsequent embolic events and survival among Japanese individuals.

Methods

Study Population

We retrospectively investigated 1,401 consecutive patients who underwent TEE at Tenri Hospital between 1995 and 2005. Patients with potential cardiac sources of emboli, including atrial septal defects or a patent foramen ovale (\(n=92\)), thrombi in the left atrium or ventricle (\(n=73\)), thoracic aortic aneurysm (\(n=49\)), vegetation (\(n=33\)) and cardiac tumors (\(n=12\)), were excluded from the study. In the remaining 1,142 patients, the presence of severe aortic plaque was evaluated, and 75 patients (6.6%) with severe aortic plaque were identified. The reasons and/or causative diseases for performing the TEE examinations are shown in Fig. 2. The incidence of subsequent embolic events and death during follow-up was examined using a medical chart review and telephone contact. The patients’ clinical courses were reviewed for up to 10 years after TEE or until death from any cause.

The study protocol was approved by the institutional ethics committee of Tenri Hospital.

Definitions

Severe aortic plaque was defined as fixed protruding plaque measuring more than 5 mm thick on TEE in the area from the aortic arch to the descending aorta\(^7\). The plaque thickness was defined as the distance between the medial-adventitial border and the lumen of the aorta measured at the maximal site.

Subsequent embolic events were defined as events including stroke, transient ischemic attack, bowel infarction, renal infarction, acute ischemia of a limb, cholesterol emboli and/or sudden death that was likely to have occurred as a result of an embolic event in the

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Fig. 1. Typical patients with severe aortic plaque on transesophageal echocardiography. (A) A 61-year-old man had severely thick plaque in the thoracic descending aorta. (B) A 65-year-old man with cholesterol embolism and multiple mobile plaques.
groups were determined using the unpaired t-test for continuous variables and Fisher’s exact test for discrete variables. The cumulative incidence of subsequent embolic events and death in each group was evaluated using a Kaplan-Meier analysis and the log-rank test. The Cox proportional hazard method was used to assess the impact of each medical therapy on the incidence of subsequent embolic events and death during follow-up. The relative risks were calculated with 95% confidence intervals (CIs). Statistical significance was set at a p value of less than 0.05.

**Transesophageal Echocardiography**

TEE was performed using a Toshiba SSH 140A Ultrasonic Unit with a 5-MHz multiplane or biplane transducer. We observed the horizontal and longitudinal views of the descending thoracic aorta and aortic arch on TEE.

**Statistical Analysis**

The statistical analysis was performed using the Statview 4 software program (Abacus Concepts, Berkeley, California). The values are expressed as the mean ± SD. Differences in parameters between two

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the study patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=75)</td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Hemodialysis</td>
</tr>
</tbody>
</table>

Age is presented as the mean ± SD.
Table 2. Characteristics of the patients who did and did not experience embolic events

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Embolic Event (n=27)</th>
<th>No Event (n=48)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>23 (85%)</td>
<td>41 (85%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Previous event</td>
<td>12 (44%)</td>
<td>10 (21%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (44%)</td>
<td>13 (27%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>22 (81%)</td>
<td>37 (77%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (52%)</td>
<td>16 (33%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>4 (15%)</td>
<td>0 (0%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9 (33%)</td>
<td>20 (42%)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Age is presented as the mean ± SD.

Table 3. Causes of death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Embolic Death</th>
<th>3 (8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Peripheral emboli</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sudden Death</td>
<td>6 (16%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac or Vascular Death</td>
<td>13 (35%)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular Death</td>
<td>15 (41%)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Results

Clinical Characteristics of the Patients with Severe Aortic Plaque

The mean follow-up period was 5.6±3.0 years. The clinical characteristics of the patients with severe aortic plaque are shown in Table 1. Among the 75 patients, 64 (85%) were men and 29 (39%) had a smoking habit at the time of TEE. Four patients (5%) were receiving hemodialysis.

The indications for TEE in the 75 patients are shown in Fig.2. The most common reason for performing TEE was to evaluate aortic lesions before surgery/catheterization.

Embolic Events

During follow-up, 27 patients (36%) experienced an embolic event: 13 strokes (17%), eight peripheral emboli (11%) and six sudden deaths (8%). The baseline characteristics of the patients who did and did not experience embolic events during follow-up are presented in Table 2.

The patients who experienced embolic events during follow-up were younger (68.0±7.2 years vs. 72.3±7.1 years, p=0.014) and had a significantly higher prevalence of previous embolic events (44% vs. 21%, p=0.03), atrial fibrillation (44% vs. 27%, p=0.04) and hemodialysis (15% vs. 0%, p=0.006) than in those who did not experience embolic events. There were no significant differences in gender, history of coronary artery disease, history of diabetes or smoking. Blood tests performed at the time of TEE showed that the white blood cell (WBC) counts, eosinophil (Eo) counts and C-reactive protein (CRP) levels were slightly higher in the patients who experienced embolic events than in those who did not experience embolic events; however, the differences were not statistically significant (WBC: 7,295±1,942 vs. 7,031±2,445/mm³, p=0.66; Eo: 355±581 vs. 217±160/mm³, p=0.15; CRP: 1.25±1.67 vs. 1.15±1.77 mg/dL, p=0.83).

Death

There were 37 deaths (49%) during the follow-up period. Death was more likely to occur in the patients who experienced embolic events (17 of 27 patients, 63%) than in the patients who did not experience embolic events (20 of 48 patients, 42%, p=0.077). The direct causes of death are listed in Table 3. The cause of death was an embolic event in 8% of the patients, sudden death in 16% of the patients, a cardiac or vascular event in 35% of the patients and a noncardiovascular event in 41% of the patients. Six sudden deaths occurred 30±30 months (3-89 months) after TEE.
Medical Treatment for Aortic Plaque

**Fig. 3.** Cumulative incidence of embolic events in patients with severe aortic plaque. Each Kaplan-Meier curve shows the incidence of embolic events in the patients treated (A) with vs. without statins, (B) with vs. without antiplatelet drugs and (C) with vs. without warfarin. HR, hazard ratio; antiPLT, antiplatelet drugs; # at risk, number of patients at risk; *p < 0.05; **p < 0.01; NS, not significant.

**Fig. 4.** Cumulative incidence of all-cause death in the patients with severe aortic plaque. Each Kaplan-Meier curve shows the incidence of all-cause death in the patients treated (A) with vs. without statins, (B) with vs. without antiplatelet drugs and (C) with vs. without warfarin. The abbreviations are the same as those in Fig. 3.
Kaplan-Meier curves for the cumulative incidence of embolic events and all-cause death in each treatment group are shown in Fig. 3 and 4. These results indicated a negative effect of warfarin administration on the incidence of embolic events and protective effects of statins and antiplatelet drugs against death. These results were obtained without background adjustment.

Multivariate Analysis
To assess the impact of each medical therapy and other clinical factors, such as atrial fibrillation, on the prognoses, a multivariate analysis was performed. As shown in Table 2, the patients who experienced embolic events during follow-up had a significantly higher prevalence of previous embolic events, atrial fibrillation and hemodialysis. Because the clinical impact of hemodialysis appeared to be larger than that of other factors, patients receiving hemodialysis were excluded from the multivariate analysis. Therefore, data regarding previous embolic events, atrial fibrillation, therapy with statins, antiplatelet drugs and warfarin and the length of follow-up were entered into a Cox proportional hazards model.

According to the multivariate Cox model analysis (Fig. 5), statin and antiplatelet drugs were independently and significantly protective against death (statin: Hemodialysis
Four of the 75 patients were on hemodialysis. During follow-up, four of these patients (100%) experienced embolic events and three (75%) died of sudden death. The prognoses of these patients were considered to be very poor, and the clinical impact of hemodialysis was quite large compared to that of other factors. Therefore, these patients were excluded from the following analysis.

Effects of Each Medical Therapy on the Incidence of Embolic Events and Death
Among the 71 patients not receiving hemodialysis, statins were administered in 36 patients (51%), antiplatelet drugs were administered in 46 patients (65%) and warfarin was administered in 28 patients (39%). Both statins and antiplatelet drugs were administered in 27 patients, both antiplatelet drugs and warfarin were administered in 19 patients and both statins and warfarin were administered in 15 patients. A combination of statins, antiplatelet drugs and warfarin was administered in 12 patients. Meanwhile, 10 patients did not receive treatment with statins, antiplatelet drugs or warfarin. There were 14 embolic events and 10 deaths in the 36 patients taking statins, 16 embolic events and 14 deaths in the 46 patients taking antiplatelet drugs and 13 embolic events and 14 deaths in the 28 patients taking warfarin.

Kaplan-Meier curves for the cumulative incidence of embolic events and all-cause death in each treatment group are shown in Fig. 3 and 4. These results indicated a negative effect of warfarin administration on the incidence of embolic events and protective effects of statins and antiplatelet drugs against death. These results were obtained without background adjustment.
Discussion

Prognoses and Medical Treatment

Among previous studies, only a few reports have discussed the optimal medical therapy for patients with severe aortic plaque on TEE\(^9, 10\). Some studies have shown that high-dose statin treatment induces the regression of aortic plaque\(^11, 12\). In addition, other studies have demonstrated that statin therapy is associated with a reduced rate of ischemic stroke\(^9, 13, 23\). With respect to anticoagulant and antiplatelet drugs, several reports have demonstrated the potential benefits of warfarin on vascular or embolic events in patients with severe aortic plaque, especially those with mobile lesions\(^15, 21\). According to guidelines\(^10, 14, 23\) published in the United States, however, evidence regarding the effects of statin, antiplatelet or warfarin therapy is not well established because no randomized trials have been completed. Furthermore, data guiding therapy for patients with severe aortic plaque among the Japanese population are lacking.

In this study, the univariate and multivariate analyses showed that both statins and antiplatelet drugs have protective effects against death, although these treatments do not have protective effects against subsequent embolic events. The beneficial effects of statins on the survival rate of patients with severe aortic plaque may be due to the pleiotropic effects of these drugs\(^24-26\), which involve plaque regression, plaque stabilization, anti-inflammatory effects and inhibitory effects on the coagulation cascade. Many patients die from concomitant complications and diseases following stroke or peripheral embolization, including aspiration pneumonia and lower limb infection. The pleiotropic effects of statins may beneficially influence these conditions.

The beneficial effects of antiplatelet drugs are also related to the ability of these drugs to prevent concomitant medical problems due to plaque rupture. Patients with severe aortic plaque have been reported to have a high prevalence of coronary artery disease and other atherosclerotic diseases\(^3, 27-30\). Statins and antiplatelet drugs may be effective in reducing the mortality rate of systemic atherosclerotic diseases, despite their lack of direct effects on reducing the incidence of embolic events. Another causative factor of why statins did not exhibit beneficial effects on the incidence of embolic events in this study may be the small number of patients. In addition, the doses of statins and the low-density lipoprotein levels were not evaluated in this study.

With regard to the effects of warfarin, no significant beneficial effects on the survival rate were observed in this study. The patients taking warfarin exhibited a higher incidence of embolic events according to the Kaplan-Meier curves (Fig. 3). However, this does not mean that warfarin is harmful in patients with severe atheromatous plaque because most of the patients taking warfarin evaluated in the univariate analysis had atrial fibrillation. The multivariate analysis showed that warfarin had neither beneficial nor harmful effects on the embolic event rate. One reason for this finding may be that warfarin does not have advantageous effects in suppressing plaque rupture. Anticoagulant therapy exhibits two different reported effects on the prognoses of patients with severe aortic plaque. Some studies have reported that anticoagulant therapy has beneficial effects on embolic events\(^19, 21\), while others have reported that atheroembolic syndromes, such as the formation of cholesterol emboli, which often develop in patients with severe aortic plaque, may worsen under anticoagulant therapy\(^15-18\). Therefore, the use of anticoagulant therapy in patients with severe aortic plaque remains controversial\(^10\). Consistent with the findings of previous reports\(^9, 10, 22\), warfarin was found to have a neutral effect on both embolic events and death in our study.

Clinical Implications

Considering our results, there is a possibility that statins and antiplatelet drugs are effective in improving the prognoses of patients with severe aortic plaque. Such patients are likely to have other atherosclerotic diseases, including coronary artery disease; therefore, it is important to assess the presence of concomitant atherosclerotic diseases and apply aggressive treatment with statin and antiplatelet drugs. Antiplatelet drugs may be effective in primary prevention among patients with severe aortic plaque who have not experienced coronary artery disease or cerebrovascular disease. On the other hand, the high incidence of embolic events in the patients taking warfarin observed in this study appeared to be associated with the presence of atrial fibrillation. Following background adjustment, warfarin did not show harmful effects on the prognosis. Therefore, the choice of whether to use warfarin in patients with severe aortic plaque may depend on the
presence of other conditions requiring anticoagulation, such as a history of atrial fibrillation or mechanical valve replacement, and warfarin does not necessarily have to be discontinued for the simple reason that a patient has severe aortic plaque.

Study Limitations
This study is associated with several limitations. First, because the study design was retrospective, the patients were not systematically followed, resulting in bias with respect to the evaluation of drug effects. Second, we did not assess the influence of other clinical factors, such as the serum low-density lipoprotein levels, underlying diseases and other medications. Third, we did not evaluate the level of international normalized ratio (INR) in each patient taking warfarin. Some patients with a low INR may have been receiving subtherapeutic doses of warfarin, which may have resulted in underestimation of the advantageous and/or disadvantageous effects of warfarin. Finally, the small number of patients is a major issue. This study was a small study that evaluated 75 patients because severe aortic plaque was observed in only 6.6% of the patients who underwent TEE at our institution. However, previous studies from other countries have also had small study populations. In addition, the current study did not estimate clinical risk factors for aortic atheroma because we did not evaluate detailed risk factors in patients without aortic plaque. Prospective studies with larger cohorts are needed to establish evidence for optimal treatment strategies in patients with severe aortic plaque.

Conclusions
This study presented data regarding the clinical courses of Japanese patients with severe aortic plaque in relation to specific medical treatments. Warfarin exhibited neither beneficial nor harmful effects on the prognosis. Treatment with statins and antiplatelet drugs may improve the prognoses of patients with severe aortic plaque.

Conflicts of Interest
None.

References


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