Cerebral Microembolization After Bioprosthetic Aortic Valve Replacement

Comparison of Warfarin Plus Aspirin Versus Aspirin Only

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Background—No human physiological data exists on whether aspirin only is as effective as warfarin plus aspirin in preventing cerebral microembolization in the early postoperative period after bioprosthetic aortic valve replacement (bAVR).

Methods and Results—We prospectively enrolled 56 patients who had no other indication for oral anticoagulation, who underwent bAVR and received, in an open-label fashion, either daily warfarin (for INR 2.0–3.0) plus 81 mg of aspirin (n=28) or 325 mg of aspirin only (n=28). Cerebral microembolization was quantified at 4 hours (baseline) and at 1 month postoperatively, by recording 1-hour bilateral middle cerebral artery (MCA) microembolic signals (MES). Platelet-function analysis (PFA) of closure times (CT) on collagen was also used as a marker of platelet-dependent activation. Follow-up to 1 year was complete. Preoperative demographics and baseline platelet function were equivalent in both groups. There was no mortality, stroke, or transient ischemic attack at 1 year in either group. No significant differences were found in the proportion of patients with MES among those receiving warfarin plus aspirin versus aspirin only, at baseline (68% versus 82%, respectively; P=0.4) and at 1 month (46% versus 43%; P=1.0) after bAVR. The total MES and PFA were also equivalent between groups, at baseline and follow-up.

Conclusions—Early after bAVR, the effects of these 2 antithrombotic regimens on cerebral microembolization and platelet function are equivalent. These data bring new mechanistic support to the premise that aspirin only may safely be used early after bAVR in patients who have no other indication for oral anticoagulation. (Circulation. 2012;126[suppl 1]:S239–S244.)

Key Words: cerebral embolization ■ anticoagulation ■ bioprosthetic aortic valve replacement

The use of biological valve prostheses for aortic valve replacement has increased in recent years because of the better quality and durability of their components.1 Although long-term results show a low incidence of thromboembolic complications, the first 3 postoperative months are considered a higher risk period for thromboemboli formation, due to the incomplete endothelialization of the sewing ring.2 The guidelines of the American College of Cardiology/American Heart Association,3 European Society of Cardiology,4 and American College of Chest Physicians5 indicate that patients undergoing bioprosthetic aortic valve replacement (bAVR) should be managed with warfarin to maintain an INR between 2.0 and 3.0 during the first 3 postoperative months, followed by daily low-dose aspirin. Although surgeons were initially supportive of these recommendations,5 recent clinical surveys suggest that only 17% of cardiac surgeons follow these guidelines after bAVR.6,7 Moreover, there is substantial uncertainty among surgeons as to which of the treatments results in the most optimal risk-to-benefit ratio.7,8 Only 4 studies have investigated the incidence of cerebral thromboembolic events after bAVR in patients treated with warfarin plus aspirin versus aspirin only. Their results are controversial. Although one study found that not using warfarin after bAVR was associated with a higher incidence of thromboembolism,9 others have documented no advantage of using oral anticoagulation on preventing thromboembolic cerebral events.7,10,11 Overall, the results of these studies have been limited by their clinical end points being documented.
only by chart review, gross clinical examination, and/or questionnaire interview.

To our knowledge, no previously published study has compared the degrees of cerebral microembolization and platelet aggregation between patients on warfarin plus aspirin versus aspirin only early after bAVR. Such physiological inference can be obtained by transcranial Doppler (TCD) examination,12 and by measurements of inhibition of platelet-induced aggregation.13,14 Previous studies12,15 have documented that TCD can reliably and noninvasively detect and quantify emboli in the cerebral circulation, by recognizing brief transient increases in the intensity of the ultrasound signal designated as microembolic signals (MES), which indicate the presence of air or solid emboli in the cerebral circulation. Similarly, several tests of platelet function have been used to evaluate the efficacy and safety of a combined therapy based on aspirin and oral anticoagulants.13,14,16 Of these tests, the most frequently used is the response of platelets to induced aggregation, in the presence of biochemical inducers such as arachidonic acid or collagen.13,14

In this study, we prospectively assessed cerebral emboli, platelet function, and clinical outcomes in 56 patients after bAVR. Patients who had no other indication for oral anticoagulation received either warfarin plus aspirin or aspirin only for the first 3 months after bAVR, in an open-label fashion.

Methods

Study Population

The study was approved by the University of Ottawa Heart Institute Research Ethics Board. Patients scheduled for primary implantation of a bioprosthetic valve in the aortic position at the University of Ottawa Heart Institute (UOHI) were considered for inclusion. Patient exclusion criteria included emergency or redo operations; patients with a history of transient ischemic attack or cerebrovascular accident; patients with carotid artery stenosis >70%; patients with previous documented thromboembolism; patients with COPD; and patients with a history or new onset of atrial fibrillation or other heart rhythm disturbances requiring anticoagulation.

Surgical Technique and Anticoagulation

All patients underwent operation for severe aortic stenosis and received prostheses that are still commercially available in North America. Prostheses were implanted and oriented according to the manufacturer’s instructions. All implants were examined by intraoperative transesophageal echocardiography; epi-aortic echocardiographic scanning was not used.

After surgery, patients received the anticoagulation treatment that was a priori recommended by their respective surgeon, as per his or her routine practice. This consisted of either (a) aspirin at a dose of 325 mg per day, or (b) a combination of aspirin at a dose of 81 mg daily and warfarin in order to maintain the international normalized ratio (INR) between 2.0 and 3.0. Treatment allocation was open-labeled and did not vary according to patient characteristics or operative findings. Patients were scheduled to be operated by the study surgeons by a case triage nursing coordinator who was not aware of the study. Treatment allocation ensured that each surgeon labeled and did not vary according to patient characteristics or

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Assessment of Platelet Function

Peripheral blood samples (20 mL) were obtained and sent to the laboratory at baseline and 1 month after bAVR, for assessment of PFA (PFA-100 Platelet Function Analyzer, Dade Behring, Deerfield, IL). Closure times on collagen with adenosine-diphosphate (ADP) and epinephrine (EPI) (PFA Trigger Solution, Collagen-EPI Test Cartridge, and Collagen-ADP Test Cartridge, Dade Behring), as well as the percentage of P-Selectin (CD62P)-positive platelets (FC 500, Beckman Coulter, Brea, CA), were measured. Details of the laboratory testing can be found in the Online Data Supplement.

Statistical Analyses

All analyses were performed with the use of STATA, version 11.2 (College Station, TX). Because the intention of the study was to demonstrate that both antithrombotic regimens are “equivalent” in preventing cerebral microembolization as detected by TCD, sample size calculations were based on the principle of demonstrating substantial equivalence between treatments.18 To this end, we used
data from Grosset et al. Assuming a standard deviation of TCD at 1 month of 5 MES, and a minimum clinically important difference between the 2 treatment groups of 5 MES, a minimum of 28 patients per treatment group (total 56 patients, including up to 20% loss to follow-up) would be necessary to demonstrate equivalence between MES counts, with a power of 90%.

A Student t test was used for analyzing continuous data, with the assumption of equal variances. A Fisher exact test was used when proportions were analyzed. The propensity score of having received aspirin only versus warfarin plus aspirin, according to patient characteristics, was calculated for each patient, and the mean propensity score was compared between treatment groups by using a Student t test. Linear regression was also used to assess whether patient characteristics predicted MES at 1 month, using the same covariables as the treatment allocation propensity model. Statistical significance was set at less than 0.05.

Results
Because all nonexcluded patients completed the study’s procedures, the study was stopped after a total of 56 patients were enrolled and followed, with each arm of the study having 28 patients. Figure 1 shows the study’s CONSORT diagram.

There was no significant difference in preoperative patient characteristics between the two groups (Table 1). None of the patients had preoperative coagulopathy, thrombocytopenia, or malignancy. There were 2 (7.1%) patients with carotid artery stenosis and 1 (3.5%) patient with vertebral artery stenosis in the warfarin plus aspirin group, compared with none in the aspirin only group. Those differences did not reach statistical significance. Preoperatively, 20 patients (71%) were taking aspirin and none was taking clopidogrel in the aspirin only group. In the warfarin plus aspirin group, 21 patients (75%) were taking aspirin, and 1 patient (3.6%) was taking aspirin and clopidogrel.

The types of procedures were equivalent in both groups: bAVR alone was performed in 16 patients from each group (57%), and the remainder had bAVR and coronary artery bypass grafting (CABG). The bioprosthetic valves used had an equivalent distribution between the 2 groups. In the warfarin plus aspirin group, 24 of the bioprostheses (86%) were Carpentier-Edwards Perimount (Edwards Lifesciences, Irvine, CA), 3 bioprostheses (11%) were Medtronic Hancock II (Medtronic, Minneapolis, MN), and 1 bioprosthesis (3%) was a Medtronic Mosaic. In the aspirin only group, 22 (79%) Perimount, 5 (18%) Hancock II, and 1 (3%) Mosaic bioprostheses were implanted. When the surgeon was asked to comment on calcification of the aortic root, 10 patients (36%) in each group were deemed to have a calcified aortic root, and 1 patient (3%) in the aspirin only group was considered to have palpable ascending aortic plaque.

The propensity of receiving either treatment was calculated for each patient, using a model incorporating the patient characteristics listed in Table 1. There was no significant difference in mean propensity score between the 2 groups.

Follow-up to 1 year was 100% complete. There was no mortality, stroke, transient ischemic attack, myocardial infarction, or respiratory insufficiency over the duration of the study. No thrombus, structural or nonstructural prosthetic anomaly was found on postimplant tranesophageal echocardiograms, and in the 23 patients who had additional postoperative echocardiograms performed as per routine practice or for specific clinical indications. On TCD, no significant differences were found in the proportion of patients who displayed MES between those receiving warfarin plus aspirin versus aspirin only, both at baseline (68% versus 82%, respectively; P=0.4) and at 1 month (46% versus 43%; P=1.0) after bAVR (Figure 2); furthermore, the percentage
of patients with MES on 100% O$_2$ was identical between the 2 groups (61% at baseline and 36% at 1 month for either group; $P=1.0$). Table 2 displays the total MES counts in the 2 treatment groups, both at baseline and at follow-up. There was no difference in 100% O$_2$ and total MES counts between groups ($P>0.4$), which was confirmed by a linear regression model that used the patient characteristics listed in Table 1 as covariables (treatment effect coefficient on total MES counts 0.66±1.03, aspirin only versus warfarin plus aspirin; 95% CI: −1.42; 2.7; $P=0.5$). Furthermore, none of the patient characteristics covariables approached statistical significance.

PFA closure times on collagen, and P-Selectin expression are shown in Table 3. At baseline, PFA closure times on collagen were equal between groups with ADP and with epinephrine. At 1 month after AVR, closure times decreased in both groups, using ADP and epinephrine; however, closure times remained equivalent between the warfarin plus aspirin versus aspirin only groups. Similarly, P-Selectin expression was equivalent between groups, both at baseline and 1 month after bAVR.

### Discussion

To our knowledge, this is the first study to prospectively compare the effects of warfarin plus aspirin versus aspirin only groups.
in preventing cerebral embolization after bAVR, in patients at low risk of thromboembolism, by using TCD and PFA as surrogates for rare clinical thromboembolic outcomes.

Preoperatively, the 2 patient groups in our study were equivalent in terms of clinical characteristics. Risk factors for thromboembolism (coagulopathy, thrombocytosis, malignancy, etc) were similarly rare in the 2 groups, and a similar proportion of patients were on aspirin preoperatively. At baseline, the number of MES counts was equivalent in both groups, as well as the percentage of patients with MES. Biochemically, the platelet function assays of closure times on collagen were also similar at baseline, using adenosine diphosphate as well as epinephrine; the same observation was made with P-Selectin expression. One month after AVR, the number of MES counts, percentage of patients with MES, as well as the platelet assays and CD62P expression remained statistically similar between the two groups. This was observed despite the fact that the procedure and valve types were proportionally similar in both groups. Furthermore, the cardiopulmonary bypass and aortic cross clamp times were statistically equivalent between both groups. An equal number of patients were subjectively judged by the surgeons to have a calcified aortic root.

Our data indicates, in the context of preoperative and intraoperative similarity between the two groups, that aspirin is as effective as warfarin plus aspirin in preventing cerebral microembolization after surgery. This gives physiological support to the widespread clinical practice of not prescribing oral anticoagulation for a period of 3 months postoperatively to patients who are otherwise at low risk for thromboembolism after bAVR, in contrast to the guidelines that are currently in effect. Indeed, using high-dose aspirin only in the early postoperative period to prevent cerebral embolization appears safe and mechanistically supported by the present data, while not presenting the added bleeding risk associated with warfarin use.

Interestingly, despite the fact that no clinical neurological events (stroke, transient ischemic attacks) were detected possibly due to the small number of patients in the study, there was a high proportion of patients with recorded MES in both groups (46% and 43% at 1 month). These could contribute to neurocognitive deficits in the short and long term that may not overtly manifest as clinical events while in hospital and during follow-up. More studies are needed to elucidate whether such a relationship exists.

MES have been detected in patients with prosthetic valves who had negative ultrasonic signals before surgery. Mechanical valve patients with higher MES counts were more likely to experience central nervous system complications than those with lower MES counts. In contrast, another study found no correlation between MES and neurological symptoms or coagulation markers. Part of the problem has been related to the presence of nitrogen bubbles generated by the process of cavitation in the mechanical valve, which escape into the systemic circulation. When these air bubbles reach the brain, they artifactually increase the counts of MES, thereby precluding the detection of solid particles. A potential solution to the problem is the administration of 100% oxygen during the TCD examination, which significantly reduces the counts of MES. This is related to the fact that oxygen inhalation suppresses air bubbles generated by the mechanical valve, but it does not have any effect on solid particles. MES have been detected in bAVR patients, but to a lesser extent than in mechanical valves. Moreover, MES in prosthetic heart valve patients have been suspected to be related with several embolic aggregates. Once a strategy is used to distinguish solid from gaseous emboli, the TCD findings have more clinical relevance. For example, Sjelland et al observed in their study that patients who had cerebrovascular symptoms after bAVR had a higher number of both solid and gaseous emboli compared with asymptomatic patients. Furthermore, the presence of solid emboli only was significantly associated with cerebrovascular events. This gives weight to the clinical significance of detecting MES using TCD.

After aortic valve replacement, platelets more than double their thromboxane formation in response to biochemical inducers, such as arachidonic acid. Furthermore, arachidonic acid-induced platelet aggregation reaches nearly 150% of its preoperative value by day 10 after AVR. These results are in concordance with the higher risk of thromboembolism observed in patients during the first weeks after valve replacement. The postoperative increased platelet aggregation is believed to be related to the increased production of young hyper-reactive platelets as a primary response to the depletion of platelets caused by cardiopulmonary bypass. In addition, Zimmerman et al, who have conducted several studies regarding the assessments of platelet function in CABG patients receiving aspirin, have documented that CABG patients insufficiently respond to aspirin in vitro, even at concentrations that exceed those in plasma after oral antiplatelet management. Therefore, to appropriately assess the antithrombotic effects of Aspirin in any clinical trial, appropriate measures of aspirin resistance should be included. The most standardized method to determine aspirin resistance is the assessment of the platelet P-Selectin (CD62P) expression as measured by flow cytometry.

Since platelets are implicated in thromboembolic complications after bAVR, we also could have considered examining the role of dual antiplatelet therapy, as aspirin only may not provide sufficient antiplatelet activity. In this regard, aspirin plus ADP antagonists have been found to be more effective than aspirin plus oral anticoagulation in preventing thrombosis of coronary stents, which brings up the question as to whether this strategy would also apply to bAVR. The Clopidogrel and Aspirin in the Prevention of Thromboembolic complications after mechanical Aortic valve replacement (CAPTA) trial studied this idea and was stopped prematurely due to an increased incidence of early aortic valve thrombosis in the dual antiplatelet group. However, it is not possible to extrapolate those results to the bAVR population, and studies need to be done to elucidate this matter. In the present study, we chose to examine warfarin plus aspirin because current guidelines indicate anticoagulation of patients for 3 months after bAVR (and aspirin only) because it is the most commonly used approach, despite the guidelines.

Limitations
A limitation of this study is the nonrandomized nature of the administration of the treatment regimen. In addition, no major
clinical end points (death, stroke, etc) were encountered despite the high proportion of patients with positive MES. In this regard, the study was not powered toward a difference in clinical end points, which are rare and whose equivalence between very large, prospectively recruited groups of patients allocated to either treatment regimen, would constitute confirmation of the mechanistic inference found in this study.

Conclusions
At 1 month after bAVR, Doppler-detected cerebral microemboli are still identified in a high proportion of patients taking either daily warfarin and low-dose aspirin or high-dose aspirin only. However, the effects of these 2 treatment regimens on cerebral microembolization rates and platelet function at 1 month after bAVR are equivalent. Therefore, this study provides mechanistic data that support the premise that aspirin only, rather than aspirin plus warfarin, may safely be used early after bAVR in patients at low risk for thromboembolism.

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SUPPLEMENTAL MATERIAL

In intubated patients, testing under conditions of 100% oxygen followed the standard ventilation settings (PEEP: 5-8 cm H\(_2\)O, FIO\(_2\): 100%, tidal volume: 6-8 ml/kg) and ventilation rates sufficient to maintain a systemic arterial oxygen saturation greater than 95% and partial pressures of carbon dioxide (CO\(_2\)) within normal values (35-45 mm Hg).

In patients who were extubated at the time of testing, 100% oxygen was administered through noninvasive positive pressure ventilation with the use of an Evita 4 (Draeger Medical, Inc., Telford, PA) or a BiPAP Vision (Respironics Inc., Murrysville, PA) ventilator. Patients were breathing spontaneously through a NIV clear facial mask. The mask was placed over the mouth and nose and held in place using an appropriate headgear or by an examiner providing downward pressure with the thumb and first finger to ensure a tight seal. The respirator was set to apply a PEEP of 5 cm H\(_2\)O while oxygen flow was set at 60 L/min and oxygen concentration at 100%. Patients were instructed to breathe normally, avoid hyperventilation or hypoventilation and to immediately give notice if breathing becomes uncomfortable or other cardio-respiratory complaints occur.

Citrated whole blood is exposed to a membrane coated with collagen (2 \(\mu\)g Type I equine) under high shear flow conditions. In addition, the membrane may also be coated with either Epinephrine (EPI - 10 \(\mu\)g) or Adenosine diphosphate (ADP – 50 \(\mu\)g). During the test, platelets will adhere to the collagen membrane, then they will become activated upon exposure to agonists such as EPI or ADP. At this point, the platelets will release the contents of their granules and this will start the process of platelet aggregation. In the PFA-100, the platelet aggregates form a thrombus that plugs the aperture in the instrument thereby diminishing and finally stopping blood flow. The PFA-100 measures the time from the start of the test until the aperture is completely plugged and it reports a time in seconds known as the Closure Time (CT). Normal reference ranges of closure times on collagen with epinephrine and adenosine diphosphate are 90-165 seconds and 63-110 seconds, respectively. Blood obtained for flow cytometry to test for CD62P positive platelets must be used within 3 hours of blood withdrawal.