CLINICAL RESEARCH   **Clinical Trials**

A Randomized Trial of Aspirin on the Risk of Embolic Events in Patients With Infective Endocarditis

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OBJECTIVES	This study examined the effect of aspirin on the risk of embolic events in infective endocarditis (IE).
BACKGROUND	Embolism is a major complication of IE, and studies in animal models have shown that platelet inhibition with aspirin can lead to more rapid vegetation resolution and a lower rate of embolic events.
METHODS	We conducted a randomized, double-blinded, placebo-controlled trial of aspirin treatment (325 mg/day) for four weeks in patients with IE to test the hypothesis that the addition of aspirin would reduce the incidence of clinical systemic embolic events. Patients with perivalvular abscess were excluded. Serial cerebral computed tomograms and transesophageal echocardiograms were obtained in a subset of patients.
RESULTS	During the four-year study period, 115 patients were enrolled: 60 assigned to aspirin and 55 assigned to placebo. Embolic events occurred in 17 patients (28.3%) on aspirin and 11 patients (20.0%) on placebo, with an odds ratio (OR) of 1.62 (95% confidence interval [CI] 0.68 to 3.86, p = 0.29). There was a trend toward a higher incidence of bleeding in the patients taking aspirin versus placebo (OR 1.92, 95% CI 0.76 to 4.86, p = 0.075). Development of new intracranial lesions was similar in both groups. Aspirin had no effect on vegetation resolution and valvular dysfunction.
CONCLUSIONS	In endocarditis patients already receiving antibiotic treatment, the addition of aspirin does not appear to reduce the risk of embolic events and is likely associated with an increased risk of bleeding. Aspirin is not indicated in the early management of patients with IE. (J Am Coll Cardiol 2003;42:775–80) © 2003 by the American College of Cardiology Foundation

Infective endocarditis (IE) is a serious medical condition that carries high mortality and morbidity (1–3). Although many patients respond favorably to medical treatment, the course of the disease may be complicated by valvular destruction, abscess formation, embolism, and heart failure.

Embolism occurring in approximately one-third of these patients remains a major complication and is one of the main causes of death (4–7). In patients already receiving antibiotic treatment, there is no proven effective medical therapy to reduce the risk of embolism (8–11).

Platelets are an integral component of the vegetation that is a hallmark of endocarditis (12–14). Recent studies in animal models suggest that aspirin may lead to more rapid

resolution of vegetation, thus reducing the embolic rate (14,15). A favorable effect of aspirin on clinical outcome was also suggested by a small observational study (16). The objective of the present study was to determine the effect of aspirin on the frequency of embolic events in patients who had native or prosthetic valve endocarditis but no evidence of perivalvular abscess.

METHODS

This was a double-blinded, placebo-controlled, randomized trial in which 18 Canadian centers and one American center participated. The patients were enrolled between July 1994 and June 1998. The investigators at each site included at least one cardiologist and one infectious disease specialist. The cardiologist screened the echocardiographic findings of patients referred for suspected endocarditis on a daily basis and reviewed the clinical records, as appropriate, to determine whether the patients had endocarditis according to predefined criteria (as described in the following text). Similarly, all patients with positive blood cultures were reviewed, and further investigations, including echocardiography, were recommended, as appropriate. This systematic approach was to ensure that potential patients were identified early and the diagnosis promptly made.

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Manuscript received December 4, 2002; revised manuscript received March 4, 2003, accepted March 12, 2003.

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Abbreviations and Acronyms
CI  = confidence interval
IE  = infective endocarditis
OR  = odds ratio
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Inclusion and exclusion criteria. Patients were eligible to participate in the study if they fulfilled the diagnostic criteria of endocarditis, which were similar but not identical to the Duke criteria (17). The diagnosis of endocarditis required the presence of two of the following three criteria: 1) multiple positive blood cultures (at least two sets) with no known extracardiac source; 2) echocardiographic evidence of vegetation, defined as a localized, mobile mass contiguous with a valve leaflet or prosthetic valve; and 3) at least two of the following clinical findings: fever, new or changing heart murmur, pre-existing heart disease, and microvascular phenomena. Patients between 16 and 80 years of age with native valve or prosthetic valve endocarditis were eligible. Exclusion criteria included patients with isolated right-sided endocarditis, echocardiographic evidence of perivalvular abscess (defined as an abnormal echolucent mass within the perivalvular tissue), probable surgical intervention within 7 days, current use of aspirin, recent or actively evolving stroke, history of gastrointestinal bleeding or active peptic ulcer disease within the past 12 months, history of a bleeding diathesis, allergic or intolerance to aspirin, and inability or unwillingness to provide informed consent.

Randomization procedure. Computer-generated, stratified (i.e., native vs. prosthetic valve and study center) randomization was completed using the SAS RANNOR module (SAS Institute Inc., Cary, North Carolina). The randomization ratio was in a 1:1 allocation, with a small block size. Adequate allocation concealment was achieved through opaque, sealed, sequentially numbered envelopes containing participant assignment at each recruitment site.

This study was reviewed and approved by the research ethics committee of all of the participating centers, and written, informed consent was obtained from all patients.

Blinding. The treating physicians as well as investigators were blinded to patient assignment. Aspirin and placebo tablets were identical in appearance. They were manufactured and donated by Merck Frosst Canada and Company (Kirkland, Quebec). The investigators could request unblinding (if knowledge of drug assignment was believed to be important to patient management) by telephoning the coordinating center at a specified phone number that was manned 24 h/day. During the conduct of the study, there were two instances of unblinding. Both occurred in patients who developed intracranial hemorrhage and were being evaluated for surgical drainage of the hematoma.

Intervention and outcomes. Eligible patients were randomized to receive either aspirin (325 mg/day) or placebo for a total duration of four weeks to test the hypothesis that aspirin can reduce the risk of embolism in patients with endocarditis by enhancing vegetation resolution (14,15). In patients with mechanical prosthetic valves, anticoagulation therapy was continued (18). The patients were seen at least twice weekly throughout their entire hospitalization. In the setting of early discharge with home intravenous antibiotic therapy, the patients were brought back for follow-up at the completion of antibiotic therapy. At each visit, a history was taken and physical examination performed to specifically look for evidence of thromboembolic events. Predefined criteria for cerebrovascular and peripheral embolism were used (see subsequent text). In patients with a suspected neurologic event, an assessment by a neurologist was requested, and a computed tomogram of the brain was performed when clinically indicated. All patients were encouraged but not required to have a baseline cerebral computed tomogram and a follow-up study at the completion of antibiotic therapy, usually four to six weeks after the baseline study. Transthoracic echocardiograms were obtained in all patients at baseline and again at the completion of antibiotic therapy. Transesophageal echocardiographic studies were encouraged but, again, not required for participation in the study. The maximum widths, lengths, and areas of the vegetations were measured off-line (19), and the valvular regurgitation was graded from 0 (no regurgitation) to 4 (severe regurgitation) (20,21).

The primary outcome was clinical embolic events involving the brain or other organs. Clinical evidence of stroke was defined as a new neurologic deficit persisting for longer than 24 h and an absence of intracerebral hemorrhage or tumor on computed tomography. Because it is difficult to definitively differentiate an embolic stroke from a nonembolic stroke, all new strokes were considered a primary outcome event for the purpose of the study. Vascular phenomena, such as cutaneous microinfarctions, were not included. Similarly, metastatic abscesses were also not considered as embolic events. The cerebral emboli on computed tomography were defined as an infarction within the territory of a cerebral artery or multiple areas of infarction. Another important outcome was cerebral hemorrhage. A cerebral hemorrhage was diagnosed as a well-defined area of high density with irregular boundaries.

Secondary outcome events included subclinical strokes detected by cerebral computed tomography, death, major or minor bleeding, valve surgery, and echocardiographic progression of valvular involvement. Major bleeding was defined as: 1) intracranial bleeding; 2) overt bleeding resulting in a decrease in hemoglobin ≥ 20 g/l or requiring blood transfusion; and 3) bleeding into a confined space, which can cause severe morbidity, such as pericardial hematoma or paraspinal hematoma. A minor hemorrhage was defined as all other overt bleeding episodes with a drop in hemoglobin <20 g/l. Bruising or oozing at the intravenous sites alone would not be qualified as minor bleeding.

Sample size. The clinical embolic rate in the placebo group was estimated to be 26%, based on our own pilot data and other published reports (4–7,22). We estimated that aspirin

Table 1. Clinical Features of Randomized Patients With Left-Sided Infective Endocarditis

	Aspirin (n = 60)	Placebo (n = 55)
Age (yrs)	54.9 ± 14.7	56.9 ± 16.7
Women	16 (26.7)	15 (27.3)
Prosthetic valve	10 (16.7)	14 (25.5)
Pre-existing native valve disease	38 (63.3)	34 (61.8)
Anticoagulation therapy	13 (21.7)	13 (23.6)
Previous endocarditis*	4 (20)	6 (26.1)
Dental procedure within 12 weeks	12 (20)	10 (18.2)
Intravenous drug use	5 (8.3)	9 (16.4)
Symptom duration (days)	34.5 ± 48.3	33.5 ± 54.3

*Based on 20 patients in the aspirin group and 23 patients in the placebo group. Data are presented as the mean value ± SD or number (%) of patients.

would reduce the embolic rate by 8.58% (33% relative reduction). To observe this difference, 184 participants had to be randomized to each intervention group (type I error rate of 5% [two-sided]; type II error rate of 20%). The trial was designed and statistically powered to incorporate an interim analysis performed by a Data Safety and Monitoring Committee. In view of the low enrollment, an interim analysis was not performed. The Data Safety and Monitoring Committee was informed of all major adverse events, such as cerebral hemorrhage.

Data analysis. An intention-to-treat approach was used to analyze the data. Odds ratios (ORs) and measures of precision (i.e., 95% confidence intervals [CIs]) were computed on all primary and secondary outcome data (23). Statistically significant intervention differences were considered at the 5% level (two-sided). Descriptive statistics were generated for each intervention group. Differences in clinical embolic event rates and cerebral hemorrhage between the two intervention groups were assessed using contingency table analyses. A preliminary examination of each valve stratum, using the Mantel-Haenzel approach, revealed no statistical differences in any outcome (all p values >0.5). Secondary outcomes were evaluated in a similar manner, using the chi-square or Student t test, depending on the scale of measurement.

RESULTS

During the four-year study period, 115 patients with left-sided endocarditis were randomized into the trial, comprising 91 patients with native valve endocarditis and 22 patients with prosthetic valve endocarditis. In the 398 patients who did not meet the inclusion criteria, the reasons were the need for cardiac surgery in the next seven days (n = 105), already on aspirin (n = 90), right-sided endocarditis (n = 66), recent or acute stroke (n = 65), perivalvular abscess (n = 38), and bleeding diathesis (n = 34). Sixty patients were randomized to receive aspirin and 55 patients were randomized to placebo. Their clinical characteristics are shown in Table 1, and the results of laboratory investigations are shown in Table 2. *Staphylococcus aureus* and *Streptococcus viridans* were common pathogens in both groups.

Table 2. Results of Investigations of Randomized Patients With Left-Sided Endocarditis

	Aspirin (n = 60)	Placebo (n = 55)
Hemoglobin (g/l)	116.5 ± 22.0*	113.4 ± 20.5†
Platelets (10⁹/l)	234.3 ± 132.0	235.1 ± 145.1†
Positive blood culture	57 (95)	49 (89.1)
Staphylococcus aureus	14 (25)	16 (32.7)
Streptococcus viridans	19 (33.9)	18 (36.7)
Other streptococci	7 (12.5)	8 (16.3)
Enterococci	9 (16.1)	2 (4.1)
Coagulase-negative staphylococci	2 (3.6)	2 (4.1)
Others	5 (8.9)	3 (6.1)
Vegetation by transthoracic echocardiography		
Aortic valve	19 (31.7)	13 (23.6)
Mitral valve	10 (16.7)	13 (23.6)
Vegetation by transesophageal echocardiography		
Aortic valve‡	22 (41.5)	23 (46)
Mitral valve§	30 (57.7)	21 (42)

*Data available for 59 patients. †Data available for 54 patients. ‡Based on 53 patients in the aspirin group and 50 patients in the placebo group. §Based on 52 patients in the aspirin group and 50 patients in the placebo group. Data are presented as the mean value ± SD or number (%) of patients.

Outcome events. The overall embolic rate was 29% for the entire group, including both randomized and nonrandomized patients. The primary and secondary outcome events between the two groups are shown in Table 3. There were no differences between the two groups in the primary outcomes of clinical embolic events or intracranial hemorrhage. Clinical embolic events occurred in 17 patients (28.3%) on aspirin and 11 patients (20.0%) on placebo (OR 1.62, 95% CI 0.68 to 3.86, p = 0.29). The central nervous system was the site of embolization in eight patients on aspirin and three patients on placebo. Overall bleeding, including major or minor episodes, was higher (p = 0.075) in the group that received aspirin (n = 17 [28.8%] vs. 8 [14.5%]; OR 1.92, 95% CI 0.76 to 4.86). Similar numbers of patients in both groups underwent valve surgery. The duration of fever on treatment was also similar between the two groups. Similar findings were obtained when only patients with native valve endocarditis were analyzed.

Cerebral computed tomograms were obtained in 84 patients at the end of therapy (43 in the aspirin group and 41 in the placebo group). There were no differences in intracerebral abnormalities between the two groups (Table 4).

Effect on vegetation. The effects of antibiotic treatment on the evolution of vegetation and valvular regurgitation were evaluated by serial transesophageal echocardiography at baseline and after four weeks of treatment in 46 patients (23 patients each on aspirin or placebo) (Table 5). The vegetation diminished in size in both groups of patients and to similar degrees. Both absolute changes and percent changes were no different between the groups. The severity of valvular insufficiency was also similar between the two groups at both time points.

Table 3. Outcome of Patients With Left-Sided Infective Endocarditis

	Aspirin (n = 59)	Placebo (n = 55)	OR (95% CI)	p Value
Embolism or intracranial hemorrhage	20 (33.9)	14 (25.5)	1.50 (0.67–3.38)	0.413
Embolism	17 (28.8)	11 (20)	1.62 (0.68–3.86)	0.287
Heart failure	23 (39.7)*	17 (30.9)	1.47 (0.68–3.20)	0.431
Renal dysfunction	13 (22)	16 (29.1)	0.69 (0.30–1.61)	0.400
Perivalvular abscess	3 (5.1)	2 (3.6)	1.42 (0.23–8.83)	1.000
Valve surgery	18 (30.5)	13 (23.6)	1.42 (0.62–3.26)	0.528
In-hospital death	4 (6.7)†	6 (10.9)	0.58 (0.16–2.19)	0.516
Duration of fever (days)	5.9 ± 0.9‡	5.3 ± 1.0	—	0.689
Major bleeding				
Intracranial	7 (11.9)	3 (5.5)	2.33 (0.57–9.52)	0.324
>20 g/l drop in hemoglobin or into confined space	9 (15)	5 (10.9)	1.76 (0.55–5.63)	0.400
Minor bleeding	8 (13.6)	2 (3.6)	4.16 (0.84–20.52)	0.096
Major or minor bleeding	17 (28.8)	8 (14.5)	1.92 (0.76–4.86)	0.075

*Data available for 58 patients. †Data available for 60 patients. ‡Data available for 54 patients. Data are presented as the number (%) of patients or mean value ± SD.
CI = confidence interval; OR = odds ratio.

DISCUSSION

In IE, embolism is a major complication that is one of the main causes of death (4–7). Despite advances in medical and surgical treatments, the incidence of embolism has remained high at about 30% (4–7,24,25). Although prophylactic surgery has been suggested to prevent embolism, this application has not been prospectively tested and generally not widely accepted.

Although circulating factors, such as antiphospholipid antibodies and coagulation factors, may play a role (26,27), vegetation detected by echocardiography remains the most consistent risk factor for the development of embolic events (4). Vegetation is made up of an aggregation of fibrin and platelets (12–14). The effects of antiplatelet agents such as sulfinpyrazone, ticlopidine, and aspirin in experimental endocarditis are generally favorable (12–15,28–30). Whether some of the agents such as aspirin possess an antibacterial effect in addition to their antiplatelet actions remains controversial (29–31). Taha et al. (16) reported that aspirin prevented vegetation growth and reduced the risk of cerebral emboli in a small study of nine patients. The findings of these studies were the basis for undertaking the present study, which is the first randomized, controlled trial to assess the effect of aspirin in patients with endocarditis. A recent study by Kupferwasser et al. (14) showed that aspirin reduced vegetation size and renal embolic lesions without an increase in major bleeding in a rabbit model of staphylo-

coccal endocarditis, further underscoring the need for a prospective study in this regard. We excluded unstable patients, including those with perivalvular abscess, because they would have an increased likelihood of requiring surgical intervention (11,12), and aspirin use may exacerbate perioperative bleeding.

The embolic rate in this trial is similar to the rates found in other studies (4–7,24,25). No difference in embolic events was observed between patients taking aspirin and those on placebo. Similar proportions of patients in both treatment groups had serial cerebral computed tomograms, and again, no differences were found between the two treatment groups in terms of intracerebral abnormalities. We did not encounter clinical embolic events in other organ systems, such as the kidneys or spleen, although routine radiologic assessment to look for embolization in these organs was not performed.

Furthermore, we were unable to demonstrate any significant effect of aspirin on the number and size of the vegetations, although there was a significant reduction in vegetation size after antibiotic treatment for four weeks in both groups. There was also no salutary effect of aspirin on valvular dysfunction.

Patients with endocarditis are prone to the development of cerebral hemorrhage, which can have multiple mechanisms, with the majority due to septic arteritis and hemorrhagic transformation of embolic infarction rather than mycotic aneurysm (32). Anticoagulation treatment with warfarin has been reported to increase the risk of cerebral hemorrhage and is not associated with a reduction in embolic events (32–35). Our findings showed that antiplatelet treatment with aspirin also likely increased the risk of major or minor bleeding. The effect of aspirin on the frequency of cerebral hemorrhage alone could not be adequately addressed because of the small number of events.

We included both native valve and prosthetic valve endocarditis in this trial because patients with prosthetic valve endocarditis have a high embolic rate, despite contin-

Table 4. Abnormal Endocarditis Findings on Cerebral Computed Tomography

	Aspirin (n = 43)	Placebo (n = 41)	p Value
Focal lesions	5 (11.6)	6 (14.6)	0.933
Multifocal lesions	5 (11.6)	4 (9.8)	0.931
Hemorrhage	7 (16.3)	2 (4.9)	0.182
Abscess	0	0	
Total	17 (39.5)	12 (29.3)	0.451

Data are presented as the number (%) of patients.

Table 5. Evolution of Vegetation Size and Valvular Regurgitation in Patients With Endocarditis After Four Weeks of Treatment

	Aspirin (n = 23)		Placebo (n = 25)	
	Baseline	**Follow-Up**	**Baseline**	**Follow-Up**
Number of vegetations	1.61 ± 0.58	1.50 ± 0.60	1.65 ± 0.93	1.68 ± 0.99
Size of vegetation*				
Width (mm)	5.6 ± 2.4	4.6 ± 2.2‡	4.5 ± 2.6	3.6 ± 2.2‡
Length (mm)	11.4 ± 6.1	9.6 ± 3.9‡	9.8 ± 5.2	8.8 ± 5.1‡
Area (mm²)	61.6 ± 44.2	43.3 ± 30.6‡	45.9 ± 50.2	35.9 ± 37.5‡
Severity of valvular regurgitation†	2.42 ± 1.10	2.42 ± 1.10	2.42 ± 1.21	2.54 ± 1.22

*In patients with multiple vegetations, the dimensions of each vegetation were measured and entered as individual data points.
†The grading system for valvular regurgitation was as follows: 0 = no regurgitation; 1 = mild; 2 = moderate; 3 = moderately severe; and 4 = severe. ‡$p < 0.05$ compared with baseline values. Data are presented as the mean value ± SD.

uation of anticoagulation (18), and the risk of excessive bleeding associated with the combined use of anticoagulants and aspirin in patients with mechanical heart valves has been reported to be quite modest (36,37). The increased risk of bleeding with aspirin was observed in patients with native and prosthetic valve endocarditis. The sample size does not allow an assessment of the differential effects of aspirin in native versus prosthetic valve endocarditis.

This study only assessed the effect of aspirin during the acute phase of endocarditis, and the long-term effect on outcomes was not determined. We believe this is appropriate, as embolic events occurred almost exclusively early in the course of the disease (5). The average duration from symptom onset to presentation was about one month, and this may explain why most of the embolic events occurred early during hospitalization (5). Whether the use of aspirin shortly after symptom onset may have different effects remains to be determined. It is plausible that aspirin may have a salutary effect if used earlier in the course of the disease. The manifestations of endocarditis are protean, and prompt diagnosis is difficult. Most patients with endocarditis are unlikely to be diagnosed and treated significantly earlier than the patients in this trial.

It may be argued that an optimal dose of aspirin may not have been used in this trial, but an optimal aspirin dose has not been established for this disease or other conditions (38). The trend for an increased risk of bleeding in our patients taking aspirin suggests that a higher dose is not advisable. A lower dose may reduce the risk of bleeding, but it is doubtful that it will have a beneficial effect on embolic events, because a lower dose would be less effective in reducing platelet fibrin aggregation (14).

Study limitations. Our study reached 31% (n = 115) of its target sample size (n = 369). It is possible that our results reflect a type II error (i.e., having insufficient statistical power to observe the hypothesized 8.58% aspirin benefit of reducing embolic events) (39). However, our results indicate that the frequency of embolic events, similar to the size we thought to be clinically meaningful, is in the opposite direction than anticipated. As such, we believe that it is very unlikely that a daily intake of 325 mg aspirin will be more effective than placebo in preventing embolism in patients with IE. These estimations also suggest that the embolic

rates could be similar in both intervention groups. The lack of a salutary effect of aspirin in these patients was collaborated by the observations regarding the cerebral abnormalities on computed tomograms and vegetation resolution on serial transesophageal echocardiograms, which were similar between the treatment groups.

Conclusions. In stable patients with endocarditis without perivalvular abscess, the addition of aspirin (325 mg) to antibiotic treatment does not appear to reduce the embolic risk, but may increase the risk of bleeding. Aspirin also does not reduce the development of cerebral lesions nor enhance vegetation resolution. Thus, aspirin is not indicated in the early management of patients with IE.

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APPENDIX

The following centers and local principal investigators participated in the Multicenter Aspirin Study in Infective Endocarditis: C. Thompson, St. Paul's Hospital, Vancouver, British Columbia, Canada; J. Jue, Vancouver General Hospital, Vancouver; D. Taylor, University of Edmonton Hospital, Edmonton, Alberta; T. Prieur, Holy Cross and Calgary General Hospitals, Calgary, Alberta; B. Cujec, Royal University Hospital, Saskatoon, Saskatchewan; A. Aboguddah, Regina General Hospital, Regina, Saskatchewan; J. Tam, Health Science Center, Winnipeg, Manitoba; L. Melendez, Victoria Hospital, London, Ontario; C. Tomlinson, Hamilton Hospitals, Hamilton, Ontario; S. Siu, The Toronto Hospitals, Toronto, Ontario; C. Joyner, Sunnybrook Health Science Center, Toronto; T. Robinson, St. Michael's Hospital, Toronto; A. Sanfilippo, Hotel Dieu and Kingston General Hospital, Kingston; K. Chan, F. Auclair, R. Saginur, P. Jessamine, Ottawa Hospital, Civic Campus (Coordinating Center), Ottawa, Ontario; M. Turek, Ottawa Hospital, General Campus, Ottawa, Ontario; G. Honos, Jewish General Hospital, Montreal, Quebec; L. Mercier, Montreal Heart Institute, Montreal, Quebec; J. Dumesnil, Laval Hospital, Laval, Quebec; and D. Hess, University of Missouri Medical Center, Columbia, Missouri.