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# Risks and Benefits of Adding Anti-Platelet Therapy to Warfarin Among Patients With Prosthetic Heart Valves: A Meta-Analysis

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**OBJECTIVES** The objective of this study was to compare the effectiveness and safety of adding dipyridamole or aspirin to warfarin among patients with prosthetic heart valves using meta-analytic techniques.

**BACKGROUND** Patients with prosthetic heart valves are at increased risk for valve thrombosis and arterial thromboembolism. Oral anticoagulation alone, or the addition of antiplatelet drugs, has been used to minimize this risk. An important issue is the effectiveness and safety of the latter strategy.

**METHODS** A combined MEDLINE and manual search was made for relevant articles from 1966 to November 1999. Standard meta-analysis techniques were used.

**RESULTS** Ten studies involving 2,199 subjects met the inclusion criteria. Compared with anticoagulation alone, the addition of an antiplatelet agent reduced the risk of thromboembolic events (odds ratio [OR]: 0.41, $p < 0.001$) and total mortality (OR: 0.49, $p < 0.001$). The risk of major bleeding was increased when antiplatelet agents were added (OR: 1.50, $p = 0.033$). For major bleeding, the comparison of trials performed before and after 1990 (OR: 2.23 and 0.88, respectively) showed that the chi-square test for heterogeneity was significant ($p = 0.025$). The latter trials used low-dose aspirin, suggesting that the risk of bleeding may be lower with contemporary low-dose (100 mg daily) aspirin.

**CONCLUSIONS** Adding antiplatelet therapy, especially low-dose aspirin, to warfarin decreases the risk of systemic embolism or death among patients with prosthetic heart valves. The risk of major bleeding is slightly increased with antiplatelet therapy. Nonetheless, the risk of bleeding appears to have diminished with the lower doses of aspirin used in the more recent trials, resulting in a favorable risk-to-benefit profile. (J Am Coll Cardiol 2001;37:569–78) © 2001 by the American College of Cardiology

Patients with prosthetic heart valves are at increased risk for both valve thrombosis and arterial thromboembolic events, including stroke (1,2). Consequently, anticoagulation therapy is used to lessen the thromboembolic risk, albeit at the expense of increased anticoagulation-associated hemorrhage. Recently, several systematic reviews have attempted to clarify the current best evidence for prosthetic valve management (3,4). As such, current recommendations tend to be very specific and are tailored to several clinical features, including prosthetic valve location and type, presence of atrial fibrillation and prior history of thromboembolism (4,5). Unfortunately, the literature supporting these recommendations is often difficult to interpret due to small numbers of patients, lack of consistent control groups and older studies with anticoagulation monitoring that predates the International Normalized Ratio (INR).

As a means of improving the efficacy of antithrombotic therapy after cardiac valve implantation, anticoagulation has been augmented with an antiplatelet agent. Although the results of some of the trials have been encouraging, showing improved effectiveness with no substantial increase in bleeding risk, the results are far from consistent (6–17). Previous meta-analyses addressing the efficacy and safety of combined antiplatelet and oral anticoagulant for prosthetic valve management were potentially limited, having reviewed either English language trials, published data (18,19) or trials using dipyridamole (20) only.

We report a meta-analysis that includes data published in abstract form and clinical trial reports in any language. The goal of this study was to create a valid synthesis of all available, methodologically sound data to further assess the safety and efficacy of combined oral anticoagulant and antiplatelet therapy versus anticoagulant monotherapy in patients with prosthetic heart valves.

## METHODS

**Study identification.** We used systematic methods to identify all published randomized controlled trials (RCT) comparing the addition of antiplatelet therapy with oral anticoagulation in patients with prosthetic heart valves (21–23). Our search strategy involved the MEDLINE database using the search terms: heart-valve prosthesis, mechanical heart-valve, thromboembolism, anticoagulant,

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**Abbreviations and Acronyms**

CI = confidence interval
INR = international normalized ratio
NNT = number needed to treat
RCT = randomized controlled trial
RRR = relative risk reduction
TE = thromboembolic events

antiplatelet and hemorrhage. The MEDLINE search was augmented by manual searches of reference lists from the individual reports, review articles, meta-analyses and consensus statements. We included reports published as manuscripts or described in abstract form in any language from January 1966 to November 1999.

**Study eligibility.** Studies were included in the meta-analysis if: 1) patients with prosthetic heart valves were enrolled, 2) there was a comparison of the addition of an antiplatelet agent to oral anticoagulation, 3) treatment groups were assigned through random allocation and 4) objective methods were used to assess for the development of major clinical outcomes or adverse consequences. Abstracts were included. Study quality, apart from the above, was not assessed. Reviewers were not blinded as to the author, journal or type of publication.

**Data extraction.** Two reviewers independently extracted data on three major outcomes: 1) rates of thromboembolism, 2) major hemorrhagic complications and 3) total mortality. The primary author's definitions for the above were accepted. In addition, the following data were extracted from each study: mean follow-up, target INR or prothrombin time ratio, antiplatelet type and dose and whether the study was single- or double-blinded. Prosthetic valve type and position were not specifically reviewed because the original publications did not consistently examine the outcomes using these variables.

**Statistical analysis.** All analyses were performed on the intention-to-treat basis. The statistical method used has been described in detail previously (24). A p value less than 0.05 (two-sided) was considered to be statistically significant. A "typical" odds ratio (OR) along with 95% confidence intervals (CI) were calculated for individual trials and for the summary results.

Chi-square tests of heterogeneity were used to assess the validity of combining trials. As these tests have low sensitivity for detecting heterogeneity, a more liberal level of statistical significance ($p < 0.1$) was assumed (25). If a test of heterogeneity was significant, a random-effect analysis was made and reported (26). In addition, for each outcome measure we also used the fixed-effects approach of Mantel Haenszel (27) and random-effects (26,28) models to estimate summary treatment effects for all studies combined. The number needed to treat to prevent one outcome event (NNT), and the expected benefit per 1,000 patients treated was estimated from fixed-effects models.

**Sensitivity analyses.** Sensitivity analyses were performed on all three outcome events. The impact of the following variables was assessed (predefined): studies published in English versus other languages, abstract versus full publication, the type of antiplatelet agent used (aspirin versus dipyridamole), whether the studies were double-blinded or not and the type of model used (29), that is, whether fixed- or random-effects.

Each study was deleted in turn to assess the impact of the individual studies on the overall results. A cumulative meta-analysis, based on chronological order, was performed to assess the robustness of treatment effects over time (30,31). To assess for the possibility of publication bias, we estimated the number of "missing and negative" trials that would have to exist and would nullify the results of the meta-analysis according to the methods of Rosenthal and L'Abbe (32,33).

## RESULTS

**Study characteristics.** Our search strategy identified 10 prospective RCTs involving 2,199 subjects that met the inclusion criteria (6–15). Study characteristics are listed in Table 1. Previous meta-analyses asking a similar question included only three (18) or four (19) of the English language published trials or only those trials in which dipyridamole (20) was used. Of the trials we identified, only three were double-blinded (6,9,14). Two French language (10,13) and one Japanese language (8) publications were identified. One trial was published in abstract form only (11). A study by Chesebro and colleagues (16) was identified but was excluded because it compared two treatment groups receiving warfarin and either aspirin or dipyridamole and did not include a treatment group randomized to no antiplatelet therapy.

Of the trials included, six involved the antiplatelet agent dipyridamole at daily doses of 400 mg (6,8), 225 mg to 400 mg (11), 375 mg (10,13) or up to 5 mg/kg (12). The remaining four trials involved aspirin at doses of 500 mg daily (7), 500 mg twice daily (9) and 100 mg daily (14,15). Since they preceded the advent of the INR, earlier trials reported ideal levels of anticoagulation as the following: elevated prothrombin times at twice normal (6), 1.9 to 3.0 times normal (11), 1.8 to 2.3 times normal (7), 25% to 35% greater than normal (10), Quick time 25% to 35% of control (13), as thrombotest equivalents (10% of normal) (9) or unspecified (12) Quick time or thrombotest equivalents. The two trials published after 1990 reported a therapeutic anticoagulation goal INR of 3.0 to 4.5 (14) and 2.5 to 3.5 (15).

Of the three main study outcomes, an arterial thromboembolic event (TE) was well defined and was the primary end point of all included trials. Definitions were similar and involved either transient or permanent cerebral ischemic injury or ultrasound or surgically confirmed other systemic arterial embolism. Reported data for major hemorrhagic

**Table 1.** Characteristics of the Studies Included in the Meta-analysis

| Study | Ref | Year | Duration | Drug | INR | n | TE Events | | Mortality | | Major Bleeding | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Treated | Control | Treated | Control | Treated | Control |
| Sullivan | 6 | 1971 | 1 | D | 3.0–4.5 | 163 | 4/79 | 12/84 | 11/79 | 10/84 | 2/79 | 0/84 |
| Altman | 7 | 1976 | 2 | A | 1.8–2.3 | 122 | 3/57 | 13/65 | 1/57 | 2/65 | 5/57 | 3/65 |
| Kasahara¶ | 8 | 1977 | 2.5 | D | * | 78 | 2/39 | 8/39 | 3/39 | 7/39 | 1/39 | 1/39 |
| Dale | 9 | 1977 | 1 | A | 2.0–2.2 | 148 | 2/75 | 10/73 | 3/75 | 6/73 | 13/75 | 5/73 |
| PACTE | 10 | 1978 | 1 | D | † | 290 | 4/136 | 8/154 | 6/136 | 21/154 | 11/136 | 5/154 |
| Rajah | 11 | 1980 | 1–2 | D | 1.9–3.0 | 165 | 3/78 | 11/87 | 2/78 | 7/87 | N/A | N/A |
| Bran | 12 | 1980 | 2 | D | ‡ | 101 | 6/58 | 8/43 | 4/58 | 6/43 | N/A | N/A |
| Starkman | 13 | 1982 | 2.5 | D | § | 259 | 5/132 | 8/127 | 5/132 | 3/127 | 9/132 | 5/127 |
| Turpie | 14 | 1993 | 2.5 | A | 3.0–4.5 | 370 | 5/186 | 13/184 | 9/186 | 22/184 | 24/186 | 19/184 |
| Meschengieser | 15 | 1997 | 2 | A | 2.5–3.5 | 503 | 7/258 | 7/245 | 9/258 | 21/245 | 6/258 | 11/245 |
| **Totals** | | | | | | | 41/1,098 | 98/1,101 | 53/1,098 | 105/1,101 | 71/962 | 49/971 |
| | | | | | | | 3.7% | 8.9% | 4.8% | 9.5% | 7.4% | 5.0% |
| **Annualized Rates** | | | | | | | 2.2% | 5.3% | 2.9% | 5.8% | 4.4% | 3.0% |

*Prothrombin time ratio 1.7; †prothrombin time ratio 1.3–1.6; ‡degree of anticoagulation not specified; §Quick time 25% to 35% of control; ¶includes data not published in the original manuscript but included in an FDA submission (22).

A = aspirin; D = dipyridamole; Duration = mean duration of follow-up in years; INR = international normalized ratio; n = total study sample size; N/A = data not available; Ref = reference; TE = thromboembolic events.

complications of anticoagulant therapy with or without antiplatelet therapy were less consistent. Three original publications provided no data on bleeding (8,11,12). Data on bleeding for the Kasahara trial were abstracted from the dipyridamole meta-analysis that included unpublished data obtained from the registration file reviewed by the U.S. Food and Drug Administration (20). Data from the Rajah article was also available from the Pouleur meta-analysis but excluded from ours because the denominator from the active treatment groups was reported as 68 rather than 78 as in the original abstract (rendering the results somewhat suspect). The Meschengieser et al. (15) trial defined significant bleeding as that causing death, requiring transfusion or hospitalization. In the Turpie et al. (14) trial, major bleeding was defined as overt hemorrhage associated with ≥20 g/L drop in the hemoglobin level, the requirement for transfusion of ≥2 units of blood or any intracranial, intraocular, intraarticular or retroperitoneal bleeding. Minor bleeding constituted either epistaxis, genitourinary bleeding or easy bruising. Two trials (7,9) did not distinguish between major and minor bleeding events. For this analysis, any intracerebral or gastroenteric bleeding event or episode of hemoptysis was taken to represent a significant hemorrhage in these two studies. One trial (6) reported only three nonfatal gastrointestinal bleeding events that were presumed to be significant.

Mortality data were explicit for nine trials and not provided in the original publication of the Kasahara trial (8); this data was abstracted from the dipyridamole meta-analysis (20) that included unpublished data (as above). One trial provided clear data on mortality associated with hemorrhage and thromboembolism but did not provide data on total deaths per treatment group (7).

**Thromboembolic events.** The results for the impact of antiplatelet agents on the risk of TE events are summarized in Table 2 and shown in Figure 1. Overall, antiplatelet agents reduced the risk of TE events with an OR of 0.41 (95% CI: 0.29 to 0.58, $p < 0.001$). The heterogeneity chi-square test was not significant ($p = 0.79$). This treatment effect corresponds to a relative risk reduction (RRR) of 57% (95% CI: 38% to 70%) and an NNT of 30 (95% CI: 19 to 62), both calculated using a fixed-effects model.

Trials were grouped according to study era (performed pre-1990 or later) and the antiplatelet agent used (dipyridamole or aspirin). The impact of antiplatelet agents was consistent across time and with the available agents (Table 3). None of the tests for heterogeneity were statistically significant. A cumulative meta-analysis by published date shows that the reduction in risk of TE was

**Table 2.** Summary Results*

| | OR‡ | 95% CI | p Value | $\chi^2$ Test of Heterogeneity p | Relative Risk Reduction* | Number Needed to Treat*† | Adjusted Benefit per 1,000* |
|---|---|---|---|---|---|---|---|
| Thromboembolic events | 0.41 | 0.29–0.58 | < 0.001 | 0.79 | 57% | 30 | 52 |
| Mortality | 0.49 | 0.35–0.67 | < 0.001 | 0.49 | 49% | 27 | 48 |
| Major bleeding | 1.50 | 1.03–2.18 | 0.033 | 0.26 | — | 68§ | — |
| Major bleeding (excluding Meschengieser) | 1.81 | 1.21–2.71 | 0.0041 | 0.76 | — | 28§ | — |

*Derived from fixed-effects models; †number needed to treat to prevent one death; ‡a typical odds ratio less than 1.0 favors antiplatelet therapy; §number needed to harm; that is, if you treat 68 or 28 patients, 1 will sustain a major bleed.

CI = confidence interval; OR = odds ratio.

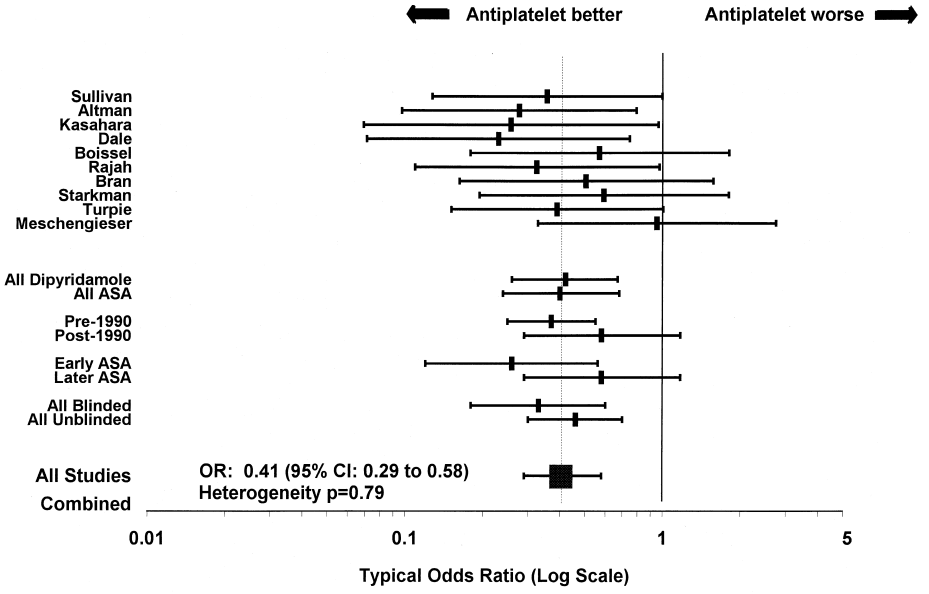


**Figure 1.** Odds ratio plots (logarithmic scale) for thromboembolism according to whether assigned to antiplatetet therapy or control. The **center of each line** represents the OR for the individual trials and subgroups with the **ends of the horizontal line** representing the 95% CIs. The **solid line** represents an OR of 1; **to the left of the line** (OR < 1) favors antiplatelet therapy, and **to the right of the line** (OR > 1) favors control or placebo. The **broken line** and the **center of the box** represent the pooled OR, and the **ends of the horizontal line** represent the pooled 95% CI. CI = confidence interval; OR = odds ratio.

robust over time and was statistically significant after the second trial. Although the magnitude of benefit diminished slightly over time, the results remained highly statistically significant. The results were not influenced by the meta-analysis technique used, whether a fixed- or random-effects model; all were highly statistically significant. In general, the CIs around the estimated treatment effect were slightly wider when using random-effects models.

**Mortality.** Data on mortality were available for all 10 trials and are shown in Table 2 and Figure 2. Total mortality was reduced with antiplatelet agents with an OR of 0.49 (95% CI: 0.35 to 0.67, $p < 0.001$). There was no evidence for heterogeneity between studies. Both aspirin and dipyridamole reduced mortality similarly. The overall effect on mortality corresponds to an RRR of 49% (95% CI: 29% to 63%) and an NNT of 27 (95% CI: 18 to 55). The effect was consistent across subgroups (Table 3, Fig. 2) and was not influenced by the type of model used. A cumulative meta-analysis showed that the magnitude of benefit was consistent over time and was statistically significant after the fifth trial.

**Table 3.** Subgroup Analyses

| | Thromboembolic Events | | | Mortality | | | Major Bleeding† | | |
|---|---|---|---|---|---|---|---|---|---|
| Trials* | OR‡ | 95% CI | p Value | OR‡ | 95% CI | p Value | OR‡ | 95% CI | p Value |
| Early DIP | 0.42 | 0.26–0.67 | < 0.001 | 0.56 | 0.36–0.87 | 0.0098 | 2.20 | 1.11–4.39 | 0.025 |
| Early ASA | 0.26 | 0.12–0.56 | < 0.001 | 0.50 | 0.16–1.61 | 0.25 | 2.41 | 1.07–5.41 | 0.034 |
| Heterogeneity $\chi^2$ | | | 0.29 | | | 0.87 | | | 0.89 |
| Pre-1990 | 0.37 | 0.25–0.55 | < 0.001 | 0.55 | 0.36–0.83 | 0.0047 | 2.23§ | 1.28–3.87 | 0.0044 |
| Post-1990 | 0.58 | 0.29–1.17 | 0.13 | 0.40 | 0.24–0.67 | < 0.001 | 0.88§ | 0.37–2.13 | 0.78 |
| Heterogeneity $\chi^2$ | | | 0.28 | | | 0.35 | | | 0.025 |
| All DIP | 0.42 | 0.26–0.67 | < 0.001 | 0.56 | 0.36–0.87 | 0.0098 | 2.20 | 1.11–4.39 | 0.025 |
| All ASA | 0.40 | 0.24–0.68 | < 0.001 | 0.42 | 0.26–0.67 | < 0.001 | 1.28 | 0.82–2.00 | 0.28 |
| Heterogeneity $\chi^2$ | | | 0.90 | | | 0.38 | | | 0.19 |
| Early ASA | 0.26 | 0.12–0.56 | < 0.001 | 0.50 | 0.16–1.61 | 0.25 | 2.51§ | 1.05–6.03 | 0.039 |
| Later ASA | 0.58 | 0.29–1.17 | 0.13 | 0.40 | 0.24–0.67 | < 0.001 | 0.88§ | 0.36–2.16 | 0.78 |
| Heterogeneity $\chi^2$ | | | 0.13 | | | 0.72 | | | 0.068 |
| Double-blind | 0.33 | 0.18–0.60 | < 0.001 | 0.59 | 0.35–1.00 | 0.049 | 1.68 | 1.00–2.84 | 0.051 |
| Not blinded | 0.46 | 0.30–0.70 | < 0.001 | 0.43 | 0.29–0.65 | < 0.001 | 1.33 | 0.78–2.27 | 0.29 |
| Heterogeneity $\chi^2$ | | | 0.38 | | | 0.36 | | | 0.59 |

*Early refers to trials performed before 1990; later trials were performed after 1990, and all used aspirin; †When comparing early dypridamole, early ASA and later ASA studies for the outcome of major bleeding, the $\chi^2$ test for heterogeneity was less than the prespecified level of significance of <0.10 (OR: 2.20, 2.41 and 0.98 respectively; $p = 0.081$). The $\chi^2$ test for heterogeneity was not significant for the outcomes of thromboembolic events ($p = 0.31$) or mortality ($p = 0.24$); ‡a typical odds ratio less than 1.0 favors antiplatelet therapy; §calculated using a random effects model as the test of heterogeneity was significant ($p < 0.10$) using the fixed effects model (28).

ASA = aspirin; CI = confidence interval; DIP = dipyridamole; OR = odds ratio.

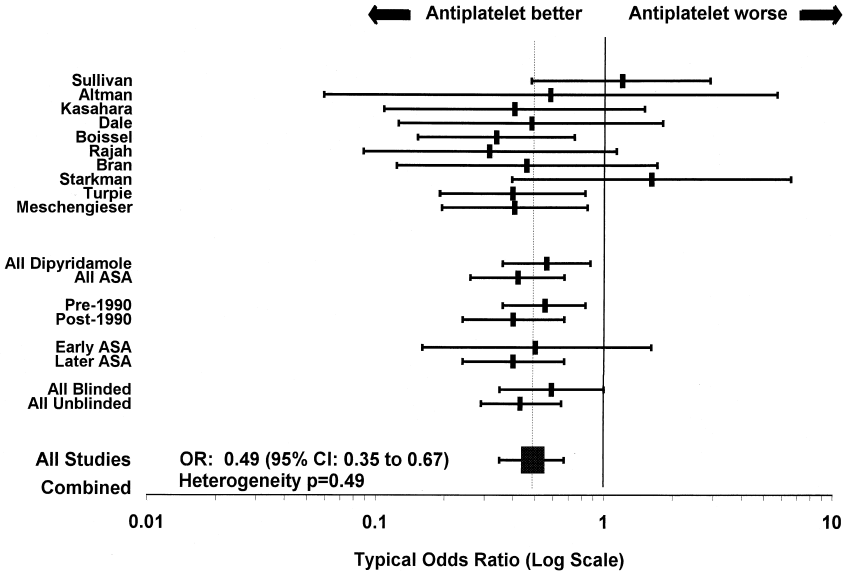


**Figure 2.** Odds ratio plots (logarithmic scale) for total mortality according to whether assigned to antiplatetet therapy or control. The **center of each line** represents the OR for the individual trials and subgroups with the **ends of the horizontal line** representing the 95% CIs. The **solid line** represents an OR of 1; **to the left of the line** (OR < 1) favors antiplatelet therapy, and **to the right of the line** (OR > 1) favors control or placebo. The **broken line** and the **center of the box** represent the pooled OR, and the **ends of the horizontal line** represent the pooled 95% CI. CI = confidence interval; OR = odds ratio.

**Major bleeding.** Data on major bleeding (Table 2, Fig. 3) were available for eight trials. There was an increase in the risk of major bleeding when antiplatelet agents were added to warfarin therapy with an OR of 1.50 (95% CI: 1.03 to 2.18; p = 0.033). The test for heterogeneity was not significant. However, the results of the analysis were influenced by the type of model used. The results were conventionally statistically significant when fixed-effects analyses were made and of borderline significance using random-effects models.

A cumulative meta-analysis (Fig. 4) showed that the risk of major bleeding became statistically significant after the third trial. Both the point estimate of bleeding risk and the degree of statistical significance, however, appeared to diminish over time and were markedly attenuated (OR from 1.81 to 1.50 and p = 0.004 to p = 0.033, respectively) with

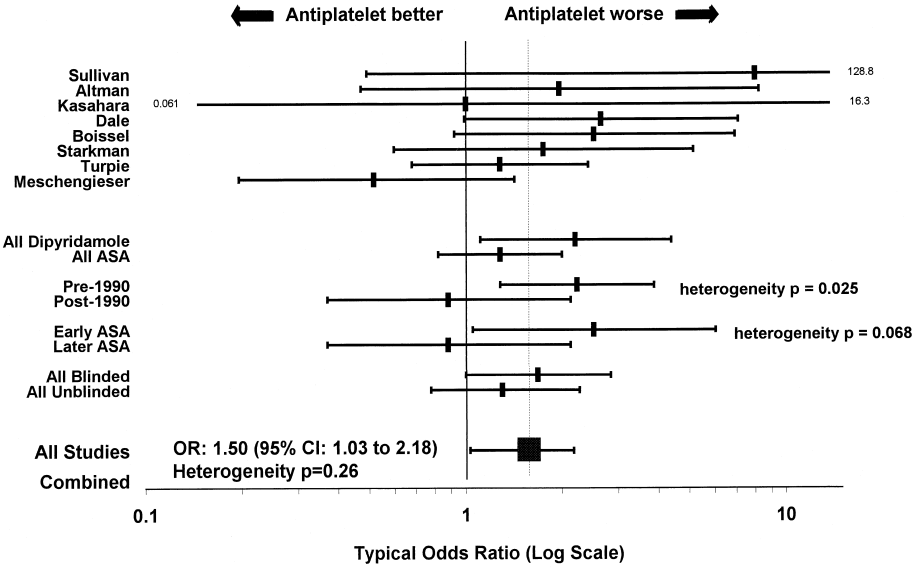


**Figure 3.** Odds ratio plots (logarithmic scale) for major bleeding according to whether assigned to antiplatetet therapy or control. Data for major bleeding was available for only eight of the trials. The **center of each line represents** the OR for the individual trials and subgroups with the **ends of the horizontal line** representing the 95% CI. The **solid line** represents an OR of 1; **to the left of the line** (OR < 1) favors antiplatelet therapy, and **to the right of the line** (OR > 1) favors control or placebo. Statistically significant tests of heterogeneity comparing pre- and post-1990 and early and late aspirin trials are shown. The **broken line** and the **center of the box** represent the pooled OR, and the **ends of the horizontal line** represent the pooled 95% CI. CI = confidence interval; OR = odds ratio.

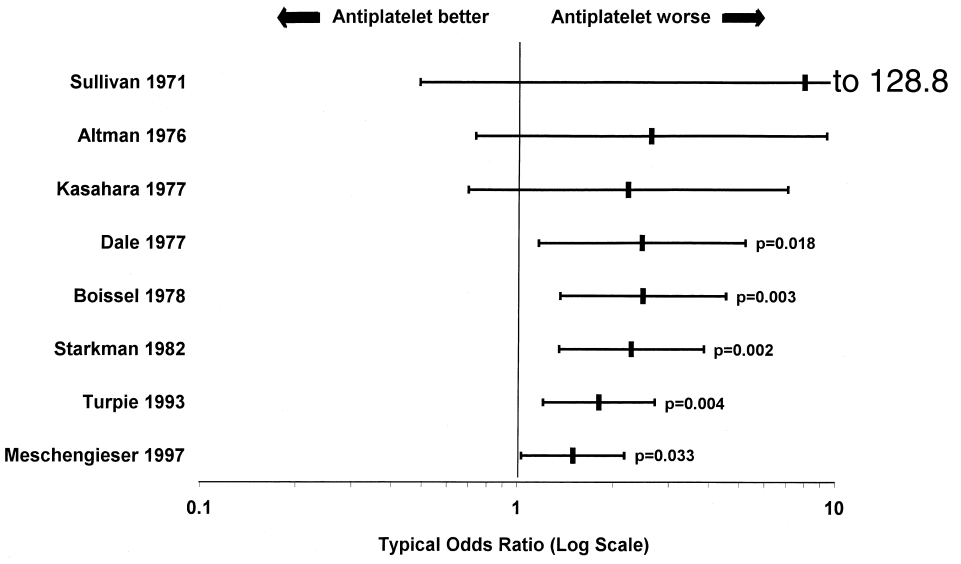


**Figure 4.** Cumulative meta-analysis of OR plots (logarithmic scale) for major bleeding according to whether assigned to antiplatelet therapy or control. The **center of each line** represents the OR for the cumulative trials with the **ends of the horizontal line** representing the 95% confidence interval. The **solid line** represents an OR of 1; **to the left of the line** (OR < 1) favors antiplatelet therapy, and **to the right of the line** (OR > 1) favors control or placebo. p values are provided for the accumulated trials once conventional statistical significance ($p < 0.05$) was achieved. OR = odds ratio.

the addition of the Meschengeiser et al. (15) trial. The latter trial was a comparison of high-dose warfarin versus the combination of low-dose aspirin and warfarin, and the risk of bleeding was not different between the two groups. Excluding this trial and repeating the analysis provided stronger evidence that the risk of bleeding was increased with antiplatelet therapy with an OR of 1.81 (95% CI: 1.21 to 2.71, $p = 0.004$, fixed-effects model) and 1.76 (95% CI: 1.16 to 67, $p = 0.008$, random-effects model).

We explored the impact of each individual trial by excluding each in turn. Excluding one aspirin trial (9) or two dipyridamole trials (10,13) rendered the risk of bleeding conventionally nonsignificant. Unpublished data on bleeding from the Kasahara trial were used in a previous meta-analysis (20) and included in ours. Repeating the analysis with this data excluded did not alter the results. The inclusion of the unpublished bleeding data from the Rajah trial (20) did influence the results. The absolute number of events for each group (four treated, seven control) were included in a sensitivity analysis. Inclusion of this small number of events lowered the OR from 1.50 to 1.39 and raised the p value from 0.033 to 0.066. Similarly, when viewing the dipyridamole trials alone, inclusion of this data lowered the OR from 2.20 to 1.63 and raised the p value from 0.025 to 0.11. Therefore, although the statistical test of heterogeneity was not significant (possibly as a result of low statistical power), there appeared to be clinical differences in the risk of bleeding between trials.

The risk of major bleeding did not differ between trials using dipyridamole and aspirin ($p = 0.19$). Nonetheless, the risk of bleeding was higher in studies performed before 1990 as compared with the two more recent trials (OR: 2.23 vs. 0.88, $p = 0.025$) (14,15). The tests for heterogeneity comparing the two later aspirin trials with either the early aspirin or the early dipyridamole trials were statistically significant ($p = 0.068$ and 0.066, respectively), again suggesting that the risk of bleeding was less in the two most recent aspirin studies. When the above subgroup analyses were repeated with the Meschengieser et al. (15) trial excluded, there was less of an impact of pre-1990 versus post-1990 trials (OR: 2.29 vs. 1.28, $p = 0.17$), dipyridamole versus all aspirin trials (OR: 2.20 vs. 1.63, $p = 0.49$) or early and later aspirin trials (OR: 2.41 vs. 1.28, $p = 0.23$).

**Additional sensitivity analyses and publication bias.** There were no differences for any of the end points among trials published in English as compared with other languages, whether published as an abstract or as a manuscript or if double-blind methodology was used or not. The Kasahara study (8) was published in Japanese and only partial data were available; the analyses were repeated with this article excluded, and the results were unchanged. As a result, the addition of unpublished data (used in a previous meta-analysis [20]) did not alter the results apart from the inclusion of the Rajah unpublished data as described above. There was no impact on the end points of TE or death when each of the other trials was also excluded in turn.

Next, a series of hypothetical variances and observed minus expected mortalities (O to E), according to the method of Peto (24) were modeled for the Kasahara trial. This showed that 25 excess deaths in the antiplatelet group as compared with the controls would have had to occur to render the overall results of the meta-analysis conventionally statistically nonsignificant. The failure to report such a massive treatment-induced mortality excess was considered highly unlikely. Moreover, unpublished mortality data from the Kasahara study, which was included in the dipyridamole meta-analysis (20), showed that mortality was nonsignificantly reduced with dipyridamole. The possibility of publi-

cation bias was assessed by the methods of L'Abbe and Rosenthal (32,33). According to the method suggested by L'Abbe, it can be shown that more than 80 small negative trials (40 per group) or 11 larger negative trials (event rate 10%, 250 per group) would have to exist to nullify the results (32). Using the method of Rosenthal (33), it was estimated that 30 to 50 negative trials would have to exist in order to nullify the results of the meta-analysis for the outcomes of death and thromboembolic events, respectively.

## DISCUSSION

The main conclusion of our meta-analysis is that the addition of an antiplatelet agent (primarily low-dose aspirin but also higher dose aspirin and dipyridamole) to warfarin in patients with prosthetic heart valves reduces the risk of death and systemic thromboembolic events. Our analysis showed that dipyridamole and aspirin seemed to reduce the risks of death and thromboembolism similarly. However, the risk of major bleeding appeared to be increased with the early dipyridamole trials as compared with the later aspirin trials where the aspirin dosage was lower, and only 100 mg daily was administered. As such, our results are in accord with the Fifth ACCP Consensus Conference on Antithrombotic Therapy where it is stated: "in view of the advantageous effects of low-dose aspirin in combination with oral anticoagulants, the indications for use of dipyridamole require further investigation" (5).

Chesebro and colleagues (16) performed a randomized trial comparing warfarin and dipyridamole (400 mg daily) to warfarin and aspirin (500 mg daily) in patients with a prosthetic heart valve replacement. The risk of TE was slightly lower, but not statistically significant, among those allocated dipyridamole (0.5 vs. 1.8 per 100 patient-years). Bleeding rates were higher among those receiving concomitant aspirin as compared with dipyridamole (6.6 vs. 1.6 per 100 patient-years, $p < 0.001$). These results are discordant with ours and may reflect the dose of aspirin chosen; 500 mg in the Chesebro study (16) as compared with the lower risk of bleeding when 100 mg daily doses of aspirin (14,15) were used.

**Aspirin effective but at less bleeding risk.** The relative effectiveness and safety of aspirin may reflect patient selection, the degree of anticoagulation (target INR) sought or the dose of aspirin used. In the comparison of the aspirin trials, the risk of bleeding in the trials performed before 1990 (7,9) (that is, before the advent of widespread use of the standardized INR) was higher even though the target INR sought in the early trials was lower compared with the post-1990 trials (14,15) (Table 1). It is our postulate that the lower risk of bleeding in the more recent trials reflects the use of lower dose aspirin: 100 mg daily in the two contemporary trials compared with 500 to 1,000 mg daily in the earlier aspirin trials. Efficacy, on the other hand, did not appear to be dependent upon the degree of anticoagulation or dose of aspirin. In this regard, a more detailed discussion of some of the two later individual trials is in order.

In the Turpie et al. double-blind randomized controlled trial (14), 186 patients were assigned to aspirin (100 mg/day delayed release, enteric coated) plus warfarin, and 184 were assigned to placebo plus warfarin. Patients were included if they had a mechanical prosthetic valve or tissue valves and atrial fibrillation or a history of thromboembolism. The target INR was 3.0 to 4.5. The primary end point (major embolism or death) was reduced among those assigned to aspirin (1.9% vs. 8.5% per year, $p < 0.001$). The stroke rate (1.3% vs. 4.2% per year, $p = 0.027$) and overall mortality (2.8% vs. 7.4%, $p = 0.01$) was reduced with aspirin. Furthermore, a composite outcome that could reflect net clinical benefit (major systemic embolism, nonfatal intracranial hemorrhage, death due to hemorrhage and vascular deaths) was also reduced with aspirin (3.9% per year vs. 9.9% per year, $p = 0.005$). Although the risk of bleeding was increased with aspirin, this was primarily due to minor bleeding including bruising, epistaxis and hematuria. Importantly, the risk of major hemorrhagic events did not differ significantly between groups (8.5% aspirin vs. 6.6% placebo, $p = 0.43$).

In the Meschengieser et al. trial (15), patients were randomized to either a high target INR (3.5 to 4.5; mean achieved 3.98) or a lower target INR (2.5 to 3.5; mean achieved 3.11) plus 100 mg of aspirin daily. The primary outcome events were rates of thromboembolism and bleeding. The rates of thromboembolism were similar at 2.8% and 2.7%, respectively. The risk of major bleeding (4.5% warfarin alone vs. 2.3% warfarin plus aspirin) and minor bleeding (17% warfarin alone vs. 14% warfarin plus aspirin) did not differ between groups but tended to favor the combination of low-dose aspirin and a lower target level of anticoagulation. Three intracranial hemorrhages occurred in the warfarin alone arm; none were seen in the combination arm. Therefore, the addition of low-dose aspirin with a lower level of anticoagulation was as effective, and possibly safer, as compared with a higher level of anticoagulation.

These results are consistent with the randomized trial by Altman et al. (17) who compared the effect of a low (INR 2.0 to 3.0) or high (INR 3.0 to 4.3) degree of anticoagulation in combination with dipyridamole (150 mg/day) and aspirin (660 mg/day) in patients with heart valve replacement. The rates of TE were similar between the low and high INR groups (1.92 vs. 4.94 per 100 patient-years, respectively) although there were very few events overall. The risk of bleeding, however, was less with the lower target INR (3.8 vs. 24.7 per 100 patient-years, $p < 0.02$). They concluded that a lower INR (2,3) used conjointly with platelet inhibitors was effective and safer than a higher target INR (17).

**Improvements over previous meta-analyses.** The first overview comparing rates of valve thrombosis, major embolism and bleeding was unable to show an advantage of the combination of aspirin and anticoagulation over anticoagulation alone; bleeding risk was increased, however (3). The studies included in the overview were not comparative randomized trials.

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The meta-analyses performed by Fiore and colleagues (18) and Cappelleri and colleagues (19) were subject to bias through inclusion of English language only trials published as full manuscripts. The Fiore meta-analysis, published in abstract form only, included four trials comparing the use of aspirin as an adjunct to oral anticoagulation. The Cappelleri meta-analysis included five trials: four involving aspirin and one involving dipyridamole. Moreover, the study by Chesebro and colleagues (16) was included in both these meta-analyses but was excluded from ours, as patients treated with warfarin were only randomized to receive either aspirin or dipyridamole. Although a control group receiving warfarin alone was subsequently included in the analysis, patients were not randomized to warfarin alone or warfarin and either of the two antiplatelet regimens (16).

The Pouleur et al. (20) meta-analysis comprised trials of dipyridamole only. It also included previously unpublished data, updated from the original publications, and a submission to the U.S. Federal Drug Agency. For the end points of TE and death, the results of our meta-analysis are in accord with theirs, and sensitivity analyses show that inclusion or exclusion of the unpublished data from published trials does not materially change our results or conclusions. The one discrepancy is for the end point of bleeding. Our meta-analysis suggests bleeding risk is increased with dipyridamole but theirs does not (OR: 2.2 vs. 1.001, respectively). The test of heterogeneity between the analyses is conventionally statistically significant (chi-square 3.968, $p = 0.046$). This may reflect our emphasis on major bleeding, whereas they included data on hemorrhagic events, whether fatal or not (20). The differences may also reflect the use of unpublished data. In this regard it is interesting to note that the bleeding risks for two of the studies (6,10) were qualitatively different in the Pouleur meta-analysis as compared with the original publications. In both original studies, the bleeding risk was slightly higher with dipyridamole; in the data used in the meta-analysis, the bleeding risk was lower. As such, our results may represent a more conservative estimate of bleeding risk.

In comparison with the above, our meta-analysis is more powerful, including data on 2,199 subjects from 10 trials and less subject to bias through inclusion of trials of any language, use of dipyridamole or aspirin and including publications as a manuscript or abstract. Furthermore, the robustness of our conclusions are reinforced through extensive sensitivity analyses which, among other things, included the impact of unpublished data, English language and other language publications (34) and whether double-blind methodology was used. None of these methodological factors impacted on our estimate of the effectiveness and safety of adjunctive antiplatelet therapy.

**Potential limitations.** Our analysis was not adjusted for study quality and, therefore, potentially at risk for this bias. A recent study found that the use of summary scores to identify trials of high methodological quality was problematic (35). Notwithstanding, it has also been shown that incorporation of studies of low methodological quality tend to show an increased estimate of benefit (36). However, our sensitivity analyses did not detect any effect of exclusion of individual trials (some of which were of lesser quality, for example the Rajah study [11], published as an abstract only) or a difference among double-blinded trials on the rates of thromboembolism or death prevention. We did not use blinded techniques during study selection or data abstraction as such procedures have not been found to be necessary (37). The possibility of publication bias in medical research is important but difficult to eliminate when performing a meta-analysis (23,38). To the present, unpublished data in meta-analyses remains controversial but should not be systematically excluded (39). Our analysis included all published data from the included randomized trials as well as some unpublished data obtained for an FDA submission and used in a previous meta-analysis (20). We were unable to verify this unpublished data. However, sensitivity analyses, excluding the unpublished data, did not alter our conclusions, except for the risk of major bleeding, as previously discussed.

We included trials that claimed to have used proper randomization techniques but did not seek to authenticate the veracity of these claims (40). Furthermore, although improper concealment of treatment allocation has been shown to be an important source of bias in RCTs (and therefore in meta-analyses based upon them), none of the included trials provided adequate information on this (41). Finally, although our study involved data on almost 2,200 subjects and the results for thromboembolism and death are highly statistically significant, there is the possibility of a type II error given the marginal degree of significance for the outcome of major bleeding. It can be shown that an individual trial of almost 3,200 subjects would be necessary to show a difference in the rate of bleeding from 5.0% to 7.4%, assuming a two-tailed alpha of 0.05 and 80% power. Pogue and Yusuf (42) have suggested that the sample size required for a meta-analysis should be at least as large as a single optimally powered RCT. As such, our analysis may be underpowered with respect to that end point only.

**Clinical implications.** Our results suggest that low-dose aspirin could be safely added to anticoagulation with an acceptable risk of bleeding and with the expectation that rates of death and thromboembolism would be reduced. Indeed, it is quite possible that outcomes would be improved with a more widespread use of aspirin as compared with existing guidelines (see Appendix). A survey performed by Ray and Turpie showed that low-dose aspirin was underused by North American cardiac surgeons. Only 21% of respondents routinely used aspirin in conjunction with anticoagulants (43). The two most common reasons for not using aspirin were the perceived increase in bleeding risk (49% of nonusers) or lack of proven benefit (23% of nonusers) (43). These concerns are unfounded and not in accord with the available trial and meta-analytic evidence.

## APPENDIX

## CURRENT RECOMMENDATIONS FOR ADDING ASPIRIN TO COUMADIN IN PATIENTS WITH PROSTHETIC HEART VALVES

According to the Fifth ACCP Consensus Conference on Antithrombotic Therapy (5), it is recommended that the addition of low-dose aspirin should be considered among:

1) patients with a mechanical valve who suffer a TE despite adequate anticoagulation;
2) those with caged ball or caged disk valve (INR target 3.0, range 2.5 to 3.5);
3) patients with mechanical valves and additional risk factors (INR target 3.0, range 2.5 to 3.5). The risk factors include: prior thromboembolism, atrial fibrillation, coronary heart disease, large left atrium, left atrial thrombus, ball valve, more than one mechanical prosthetic valve or a mechanical prosthetic valve in the mitral position;
4) a lower level of anticoagulation (INR 2.5, range 2.0 to 3.0) along with low-dose aspirin rather than a target INR of 3.0 in patients with tilting disk or bileaflet mechanical valves in the mitral position or bileaflet mechanical valves in the aortic position plus atrial fibrillation.

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