Combined Aspirin–Oral Anticoagulant Therapy Compared With Oral Anticoagulant Therapy Alone Among Patients at Risk for Cardiovascular Disease

A Meta-analysis of Randomized Trials

Francesco Dentali, MD; James D. Douketis, MD, FRCPC; Wendy Lim, MD, FRCPC; Mark Crowther, MD, MSc, FRCPC

Background: For patients receiving oral anticoagulant (OAC) therapy, deciding whether to add aspirin to their treatment is a common clinical scenario with no clear guidelines to aid practice. We performed a systematic review and meta-analysis of randomized controlled trials comparing these 2 treatment strategies (combined aspirin-OAC therapy vs OAC therapy alone) to assess the therapeutic benefits and risks.

Data Sources: Randomized controlled trials published up to June 2005 in MEDLINE, EMBASE, and Cochrane Library databases.

Study Selection: Randomized controlled trials with at least 3 months of follow-up that compared aspirin-OAC therapy with OAC therapy alone, in which OAC was administered to achieve the same target international normalized ratio or was given at the same fixed dose in both treatment arms.

Data Extraction: Two reviewers independently extracted data on study characteristics and outcomes. Pooled odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated for study outcomes in patients receiving aspirin-OAC therapy and OAC therapy alone.

Data Synthesis: Ten studies were included, totaling 4180 patients. The risk for arterial thromboembolism was lower in patients receiving combined aspirin-OAC therapy compared with OAC therapy alone (OR, 0.66; 95% CI, 0.52-0.84). However, these benefits were limited to patients with a mechanical heart valve (OR, 0.27; 95% CI, 0.15-0.49). There was no difference in the risk for arterial thromboembolism with these treatments in patients with atrial fibrillation (OR, 0.99; 95% CI, 0.47-2.07) or coronary artery disease (OR, 0.69; 95% CI, 0.35-1.36). There was no difference in all-cause mortality with either treatment (OR, 0.98; 95% CI, 0.77-1.25). The risk for major bleeding was higher in patients receiving aspirin-OAC therapy compared with OAC therapy alone (OR, 1.43; 95% CI, 1.00-2.02).

Conclusion: Our findings question the current practice of using combined aspirin-OAC therapy except in patients with a mechanical heart valve, given the questionable benefits in reducing thromboembolic events and the increased risk of major bleeding.

Arch Intern Med. 2007;167:117-124

COMBINATION ANTITHROMBOTIC therapy consisting of low-dose aspirin (≤100 mg/d) and an oral anticoagulant (OAC) is recommended only for patients with a mechanical prosthetic heart valve.[1] Despite this recommendation, a considerable number of patients with chronic atrial fibrillation receive combined aspirin-OAC therapy. In 2 recent multinational clinical trials involving patients with chronic atrial fibrillation, 25% of patients were receiving aspirin in addition to OAC therapy.[2]

Despite a lack of evidence for therapeutic efficacy, some experts have suggested that adding aspirin to OAC therapy might be useful in these patients because patients receiving OAC therapy frequently have concomitant coronary artery disease (CAD) or are at high risk for stroke.[3,4] In such patients, coadministration of an antiplatelet drug and an OAC may reduce the risk of thromboembolic and other cardiovascular events through complementary antithrombotic effects. Although combined aspirin-OAC therapy is widely used in these patients, the American College of Chest Physicians Consensus Group does not provide recommendations regarding combination therapy in patients with chronic atrial fibrillation and concomitant CAD or those patients at high risk for stroke[4] and suggests that combined aspirin-OAC therapy be used only in some patients who have a mechanical prosthetic heart valve (patients with caged

Author Affiliations:
Department of Medicine, McMaster University, and St Joseph's Healthcare, Hamilton, Ontario.

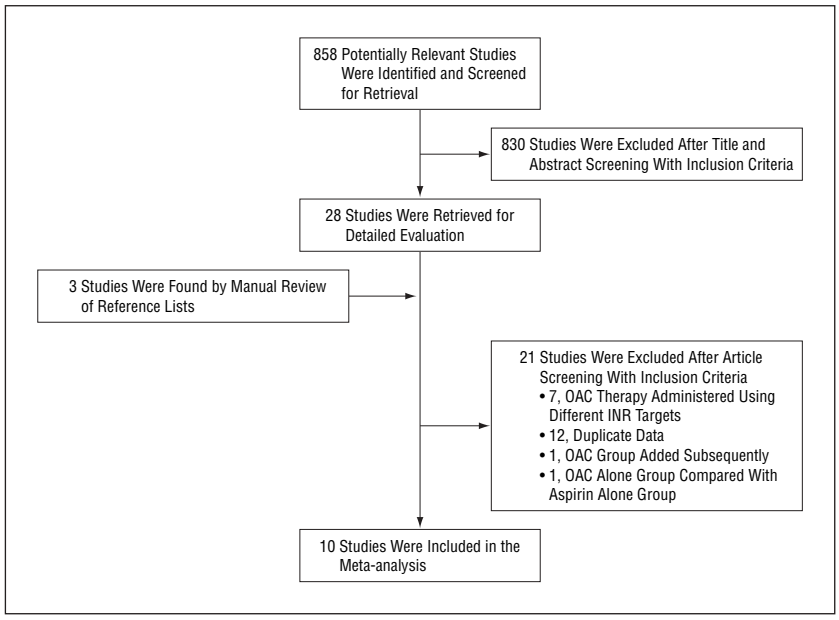

Figure 1. Study selection process. INR indicates international normalized ratio; OAC, oral anticoagulant.

ball or caged disk valves, patients with systemic embolism despite therapeutic international normalized ratio [INR], and patients with additional risk factors such as atrial fibrillation or myocardial infarction).[1] Furthermore, aspirin therapy is an established risk factor for bleeding in patients who are receiving an OAC, and patients who receive combined aspirin-OAC therapy may be receiving a potentially harmful treatment without evidence for better efficacy compared with OAC therapy alone.[5-8]

Against this background, we performed a systematic review and meta-analysis of randomized trials comparing combined aspirin-OAC therapy with OAC therapy alone. Our objective was to determine if, for selected patients receiving OAC therapy, the current practice of adding aspirin to their treatment was supported by evidence that assessed the efficacy (arterial thromboembolism) and safety (major bleeding) of this treatment approach.

METHODS

DATA SOURCES

Study Selection

We searched the MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005) and Cochrane Central Register of Controlled Trials (2005, issue 2) databases. The search strategy was supplemented by manually reviewing reference lists and by contacting content experts. Included studies assessed a broad spectrum of patients, irrespective of the clinical indication for antithrombotic therapy because the outcomes of interest are applicable to all patients who are receiving antithrombotic therapy.

Included studies satisfied the following 4 criteria: (1) randomized controlled trial in adult patients requiring OAC therapy; (2) compared combined aspirin-OAC therapy with OAC therapy alone, in which OAC therapy was administered to achieve the same target INR or was given with the same fixed dose in both treatment arms; (3) patients were followed up for 3 months or longer; and (4) at least 1 prespecified outcome (arterial thromboembolism, mortality, or major bleeding) was objectively documented. In studies with multiple publications, data were extracted from the most recent publication and, if required, earlier publications were used only to provide missing data.

Study Quality Assessment

Two reviewers (F.D. and W.L.), masked to the study authors and journals in which the studies were published, independently assessed study quality using a validated scale based on the following criteria[9]: methods used to generate the randomization sequence, method of double blinding, and description of patient withdrawals and dropouts. A score of 1 point was given for each criterion satisfied, for a maximum of 4 points. Studies with a score higher than 2 were considered high quality and studies with a score of 2 or lower were considered low quality. Although concealed treatment allocation is not part of this rating scale, it is an important aspect of randomization and was included in our study quality assessment.[10]

DATA EXTRACTION

Two reviewers (F.D. and W.L.), masked to the study authors and journals in which the studies were published, independently extracted data for arterial thromboembolism, all-cause mortality, and major bleeding. Arterial thromboembolism was defined as myocardial infarction, unstable angina requiring hospitalization, stroke, transient ischemic attack, or systemic embolism. All-cause mortality was defined as death from any cause. Major bleeding was defined as bleeding that required transfusion of 2 or more units of packed red blood cells, involved a critical site (eg, intracranial), or was fatal.[2,11] If outcome data could not be extracted, the study authors were contacted by e-mail, with a reminder after 15 days. Disagreements regarding data extraction were resolved by consensus and discussion with a third reviewer (J.D.D.).

STATISTICAL ANALYSES

The κ statistic was used to assess agreement between reviewers for study selection and quality.[12,13] Pooled odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method for arterial thromboembolism (with a separate analysis for fatal thromboembolism),[14] all-cause mortality, and major bleeding (with separate analyses for intracranial and fatal bleeding) outcomes in patients receiving aspirin-OAC therapy and OAC therapy alone, using Review Manager statistical software (RevMan version 4.2.7; The Cochrane Collaboration, Oxford, England; 2004). The appropriateness of pooling the results from individual studies was assessed using the I^2 test for heterogeneity.[15] The I^2 value describes the percentage of total variation across studies due to heterogeneity rather than chance. All analyses were initially done using a fixed-effects model, and if heterogeneity across studies was observed, the analyses were repeated using a random-effects model, which includes a measure of variance in the cal-

Table 1. Study Characteristics Comparing the Therapeutic Benefits and Risks of Combined Aspirin-OAC Therapy vs OAC Therapy Alone

Source	Indication for Oral Anticoagulation	Patients, OAC Group/ OAC + Asp Group, No.	Age, OAC Group/OAC + Asp Group, Mean (SD), y	Target Range of OAC	Aspirin Dose, mg/d
Altman et al,[48] 1976	Mechanical valves	65/57	NR	TT, 1.8-2.3 times the normal level	500
Dale et al,[46] 1980	Mechanical valves	73/75	51.4 (3.5)/50.1 (3.5)	TT, 10%	1000
Cohen et al,[42] 1990	UA, non Q-wave MI	24/37	61 (NR)/63 (NR)	INR, 3.0-4.5	80
Meade et al,[45] 1992	Primary prevention in high-risk men	1277/1268	57.6 (6.8)/57.4 (6.9)	INR <1.5	75
Turpie et al,[41] 1993	Mechanical valves	184/186	58.1 (NR)/58.1 (NR)	INR, 3.0-4.5	100
Gullov et al,[31] 1999	Chronic non valvular AF	167/171	74.2 (7.7)/72.7 (8.2)	1.25 mg/d (Warfarin)	300
Laffort et al,[27] 2000	Mechanical valves	120/109	63 (NR)/63 (NR)	INR, 2.5-3.5	200
Huynh et al,[24] 2001	Secondary prevention in patients with ACS and CABG	45/44	67 (12)/66 (12)	INR 2.0-2.5	80
Lechat et al,[25] 2001	AF with previous TE event or age ≥65 y with hypertension, HF, or EF <40%	81/76	74.1 (6.8)/73.3 (5.7)	INR, 2.0-2.6	100
Casais et al,[22] 2002	Mechanical valves	64/57	57.6 (NR)/56.9 (NR)	INR, 2.4-3.6	100

Abbreviations: ACS: acute coronary syndrome; AF: atrial fibrillation; Asp, aspirin; CABG, coronary artery bypass graft surgery; EF, ejection fraction; HF, heart failure; INR, international normalized ratio; MI, myocardial infarction; NR, not reported; OAC, oral anticoagulant; TE, thromboembolic; TT, thrombin time; UA, unstable angina.

culation of pooled results.[16] A sensitivity analysis was done in high-quality studies to assess the robustness of findings from the primary analyses. Publication bias was assessed using a funnel plot of effect size against standard error.[17]

Subgroup analyses were done to assess the efficacy and safety of aspirin-OAC therapy and OAC therapy alone according to the clinical indication for OAC therapy (atrial fibrillation, mechanical heart valve, and CAD).

RESULTS

DATA SOURCES

Study Selection

As shown in **Figure 1**, 858 potentially eligible studies were identified, of which 830 were excluded after reviewing the study abstracts, leaving 28 studies for a more detailed evaluation.[18-45] Three additional studies were identified through a manual review of study bibliographies.[46-48] Communication with 5 content experts did not identify any additional eligible studies. Of these 31, 21 were excluded for the following reasons: duplicate data in 12 studies* ; different intensities of OAC therapy were administered in the 2 treatment arms in 7 studies[18-20,29,36,38,39]; OAC was compared with aspirin alone in 1 study[40]; and the OAC group was not part of the original protocol but was added subsequently in 1 study.[44] In total, 10 studies were therefore included in this meta-analysis.† The interobserver agreement for study selection was excellent, with $\kappa = 0.99$.

Study Characteristics and Quality

The main characteristics of the included studies are given in **Table 1**. All included studies were published in English. A total of 4180 patients were studied, with study sample sizes ranging from 61 to 2545 patients. There were 5 studies of patients with mechanical heart valves,[22,27,41,46,48] 2 studies of patients with atrial fibrillation,[25,31] 2 studies of patients with CAD,[24,42] and 1 study involving patients at high risk for cardiovascular disease.[32] Low-dose aspirin (≤100 mg/d) was used in 6 studies[22,24,25,32,41,42] and moderate to high-dose aspirin (200-1000 mg/d) in 4 studies.[27,31,46,48] In 8 studies, the target INR was 1.8 or higher,[22,24,25,27,41,42,46,48] while in the remainder it was 2.0 or higher.

As given in **Table 2**, 4 studies were rated as high quality[24,25,32,41] and 6 studies were rated as low quality.[22,27,31,42,46,48] All studies had appropriate random allocation of treatment, 5 studies were double blind,[24,25,32,41,46] 6 studies provided a description of patient withdrawals,[24,25,27,32,41,42] and 3 studies had concealed treatment allocation.[24,32,41]

DATA SYNTHESIS

Primary Analyses

Data relating to the primary study outcomes (arterial thromboembolism, all-cause mortality, and major bleeding) and secondary study outcomes (fatal arterial thromboembolism, and fatal major bleeding) are documented in **Table 3**.

Arterial Thromboembolism. Arterial thromboembolism occurred in 128 (6.3%) of 2023 patients who received aspirin-OAC therapy and 179 (8.8%) of 2036 patients who received OAC therapy alone. The risk for arterial thromboembolism was significantly lower with aspirin-OAC therapy than with OAC therapy (OR, 0.66; 95% CI, 0.52-0.84; absolute risk reduction, 2.5%; number needed to treat, 40). Ow-

*References 21, 23, 26, 28, 30, 33-35, 37, 43, 45, and 47.

†References 22, 24, 25, 27, 31, 32, 41, 42, 46, and 48.

Table 2. Study Quality Assessment Comparing the Therapeutic Benefits and Risks of Combined Aspirin-OAC Therapy vs OAC Therapy Alone

Source	Properly Randomized	Concealed Treatment Allocation	Double-blind	Description of Withdrawals	Quality Rating
Altman et al,[48] 1976	Yes	NS	No	No	Low
Dale et al,[46] 1980	Yes	NS	Yes	No	Low
Cohen et al,[42] 1990	Yes	NS	No	Yes	Low
Meade et al,[45] 1992	Yes	Yes	Yes	Yes	High
Turpie et al,[41] 1993	Yes	Yes	Yes	Yes	High
Gullov et al,[31] 1999	Yes	NS	No	No	Low
Laffort et al,[27] 2000	Yes	NS	No	Yes	Low
Huynh et al,[24] 2001	Yes	Yes	Yes	Yes	High
Lechat et al,[25] 2001	Yes	NS	Yes	Yes	High
Casais et al,[22] 2002	Yes	NS	No	No	Low

Abbreviations: NS, not specified; OAC, oral anticoagulant.

ing to heterogeneity across studies for this outcome ($P=.02$), the analysis was repeated using a random effects model with no effect on the results (OR, 0.57; 95% CI, 0.34-0.93). There was no difference in the risk for fatal arterial thromboembolism (OR, 1.08; 95% CI, 0.76-1.53) (**Figure 2**).

All-Cause Mortality. There was no significant difference in all-cause mortality in patients receiving aspirin-OAC therapy compared with OAC therapy alone (OR, 0.98; 95% CI, 0.77-1.25; $P=.88$) and no significant heterogeneity across studies ($P=.20$) (**Figure 3**).

Major Bleeding. Major bleeding occurred in 80 (3.8%) of 2080 patients who received aspirin-OAC therapy and 60 (2.8%) of 2100 patients who received OAC therapy alone. The risk for major bleeding was significantly higher in patients receiving aspirin-OAC therapy (OR, 1.43; 95% CI, 1.00-2.02; absolute risk increase, 1.0%; number needed to harm, 100). Systematic analysis identified no statistically significant differences in the risk for intracranial bleeding (OR, 1.36; 95% CI, 0.55-3.32), or fatal bleeding (OR, 1.20; 95% CI, 0.42-3.46). There was no significant heterogeneity across studies for this outcome ($P=.67$) (**Figure 4**).

Sensitivity Analyses. The results of the primary analyses were supported by the sensitivity analyses performed in 4 high-quality studies.[24,25,32,41] Compared with patients who received OAC therapy alone, patients who received aspirin-OAC therapy had a lower risk for arterial thromboembolism (OR, 0.70; 95% CI, 0.52-0.93), and a documented trend toward increased major bleeding (OR, 1.38; 95% CI, 0.85-2.25). All-cause mortality did not appear to differ in the 2 treatment groups (OR, 0.97; 95% CI, 0.75-1.26).

Publication Bias. This was assessed with 3 funnel plots, which are available from the authors on request. These included 9 studies because 1 study did not provide data on thromboembolic events,[22] 1 study had no bleeding events,[42] and 1 study had no deaths.[22] The funnel plots for thromboembolic, mortality, and bleeding outcomes appeared symmetric, suggesting the absence of publication bias.

Secondary Analyses in Patient Subgroups

In patients with a mechanical heart valve, there was a significantly lower risk for arterial thromboembolism in patients who received aspirin-OAC therapy compared with OAC therapy alone (OR, 0.27; 95% CI, 0.15-0.49). There was no statistically significant difference in the risk for arterial thromboembolism with these treatments in patients with atrial fibrillation (OR, 0.99; 95% CI, 0.47-2.07) or CAD (OR, 0.69; 95% CI, 0.35-1.36). There was no difference in mortality between the 2 treatment groups in patients with atrial fibrillation (OR, 1.24; 95% CI, 0.50-3.04), in patients with a mechanical heart valve (OR, 0.66; 95% CI, 0.38-1.13), and in patients with CAD (OR, 0.86, 95% CI, 0.15-4.90). In patients with a mechanical heart valve, there was a significantly higher risk for major bleeding in patients who received aspirin-OAC therapy compared with OAC alone (OR, 1.49; 95% CI, 1.00-2.23). The risk for bleeding was not significantly different between treatments in patients with atrial fibrillation (OR, 1.02; 95% CI, 0.25-4.09). The data for bleeding outcomes in the 2 studies involving patients with CAD were not pooled because the OR for bleeding could not be calculated for 1 of the studies in which no bleeding events were documented.[24,42]

COMMENT

This study demonstrates that there is little support in the published literature for the common clinical practice of adding aspirin to OAC therapy except in selected patients with a mechanical heart valve.

The finding that aspirin-OAC therapy is associated with a lower risk for arterial thromboembolism compared with OAC therapy alone appears to be driven by the results of 3 trials in patients with a mechanical heart valve[41,46,48] and 1 trial assessing the primary prevention of cardiovascular disease in high-risk patients.[32] Data from the secondary analyses that compared combined aspirin-OAC therapy and OAC therapy alone according to the indication for anticoagulation showed a significantly lower risk for nonfatal arterial thromboembolism in patients with a mechanical heart valve but not in patients with atrial fibrillation or CAD. Furthermore, the primary analysis found no difference in mortality between aspirin-OAC therapy and OAC therapy alone, regardless of the patient level of risk.

Only 2 small randomized trials addressed the issue of combining aspirin and OAC therapy in patients with atrial fibrillation.[25,31] These trials provide conflicting results: one trial (157 patients) found that, compared with OAC therapy alone, as-

Table 3. Study Outcomes Comparing the Therapeutic Benefits and Risks of Combined Aspirin-OAC Therapy vs OAC Therapy Alone

Source	Indication for Anticoagulation	Patients, OAC Group/ OAC + Asp Group, No.	Mean Follow-up, OAC Group/ OAC + Asp Group, mo	Primary Outcome	Total TE Events. OAC Group/ OAC + Asp Group, No.	Total Deaths, OAC Group/ OAC + Asp Group, No.	Major Bleeding Events, OAC Group/ OAC + Asp Group, No.
Altman et al,[48] 1976	Mechanical valves	65/57	22.5/24.7	TE episodes (stroke, TIA, and MI)	13/3	2/1	7/7
Dale et al,[46] 1980	Mechanical valves	73/75	24/24	TE episodes (stroke, TIA, MI, and peripheral arterial embolism)	12/2	6/3	5/7
Cohen et al,[42] 1990	UA, Non-Q wave MI	24/37	3/3	Composite: recurrent myocardial ischemia, MI, and total death	10/16	1/0	0/0
Meade et al,[45] 1992	Primary prevention in high risk men	1268/1277	82/82	Composite: coronary death, fatal, and nonfatal MI	83/71	95/103	9/12
Turpie et al,[41] 1993	Mechanical valves	184/186	30/30	Composite: death from vascular causes, major systemic embolism, valve thrombosis, and clinically important hemorrhage	17/7	22/9	19/24
Gullov et al,[31] 1999	Chronic nonvalvular AF	167/171	26/26	Composite: stroke (ischemic or hemorrhagic), and systemic TE event	14/12	6/8	3/1
Laffort et al,[27] 2000	Mechanical valves	120/109	12/12	Composite: death, major TE events, and major hemorrhage	20/32	5/10	10/21
Huynh et al,[24] 2001	Secondary prevention in patients with ACS and CABG	45/44	12/12	Composite: death and MI or UA requiring new hospitalization	18/11	1/2	1/2
Lechat et al,[25] 2001	AF with previous TE event or ≥65 y with hypertension or HF or EF<40%	81/76	10/10	Combination: stroke (ischemic or hemorrhagic), MI, systemic arterial emboli, and vascular death	2/5	3/3	1/3
Casais et al,[22] 2002	Mechanical valves	64/57	17/20	INR variability	NR	0/0	5/3

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; Asp, aspirin; CABG, coronary artery bypass graft surgery; EF, ejection fraction; HF, heart failure; ICH, intracranial hemorrhage; INR, international normalized ratio; MI, myocardial infarction; NR, not reported; OAC, oral anticoagulant; TE, thromboembolic; TIA, transient ischemic attack; UA, unstable angina.

pirin-OAC therapy was associated with a nonsignificantly higher risk for arterial thromboembolism (OR, 3.29; 95% CI, 0.33-32.3)[25]; the other trial (328 patients) found that aspirin-OAC therapy was associated with a nonsignificantly lower risk for arterial thromboembolism (OR, 0.82; 95% CI, 0.37-1.84).[31] Only 1 trial was found to be of high quality,[25] and neither study used the currently recommended therapeutic INR range between 2.0 and 3.0.

In contrast, 5 trials involving almost 1000 patients compared aspirin-OAC therapy with OAC therapy alone in patients with a mechanical prosthetic heart valve.[22,27,41,46,48] In such patients, the use of aspirin-OAC therapy was associated with a significant reduction in the risk for arterial thromboembolism, although the risk for major bleeding appeared to be increased.

Our finding that aspirin-OAC therapy is associated with an increased risk for major bleeding is consistent with previous studies.[2] Combined antithrombotic therapy, consisting of aspirin and OAC, aspirin and clopidogrel, or aspirin and dipyridamole, is known to increase the risk for bleeding compared with the use of a single antithrombotic agent.[8,49,50] In a recent study that assessed 3566 patients with chronic atrial fibrillation who were receiving warfarin therapy targeted to achieve an INR of 2.0 to 3.0, patients who were receiving concomitant aspirin (≤100 mg/d) had a more than 2-fold increased risk for major bleeding (OR, 2.41; 95% CI, 1.69-3.43).[2]

There are potential weaknesses of our meta-analysis. The definition of arterial thromboembolism varied across studies. However, all events were clinically detected and associated with either direct morbidity and mortality (myocardial infarct and stroke) or the potential for increased future morbid events (unstable angina and transient ischemic attack). In addition, the criteria for major bleeding varied across studies. We attempted to overcome this

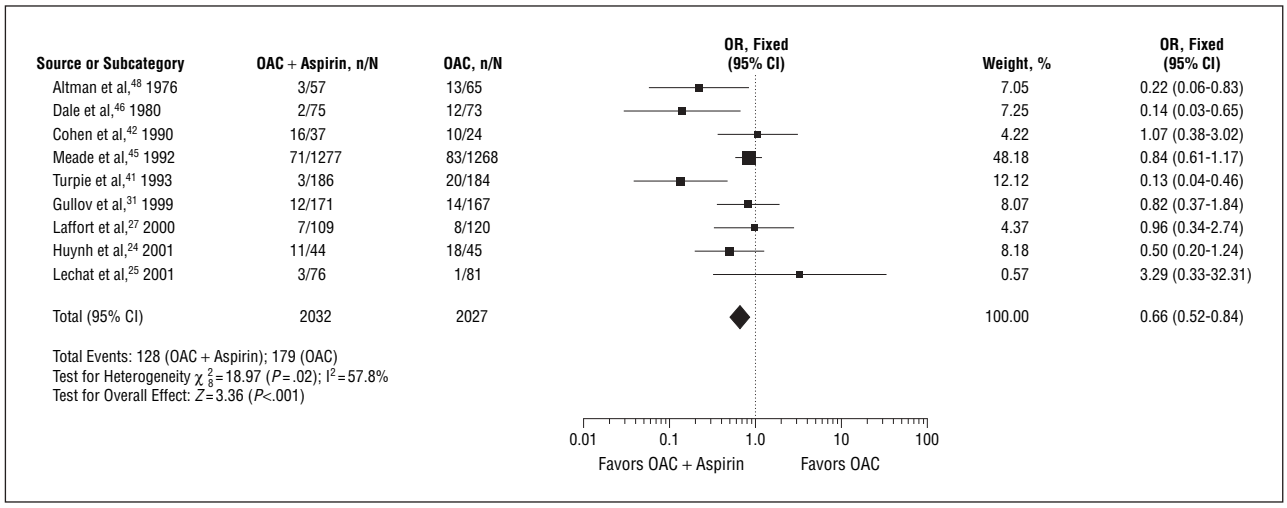

Figure 2. Risk for arterial thromboembolism in patients receiving aspirin + oral anticoagulant (OAC) therapy or OAC therapy alone. CI indicates confidence interval; n/N, number of patients at risk/total number of patients in treatment group; and OR, odds ratio.

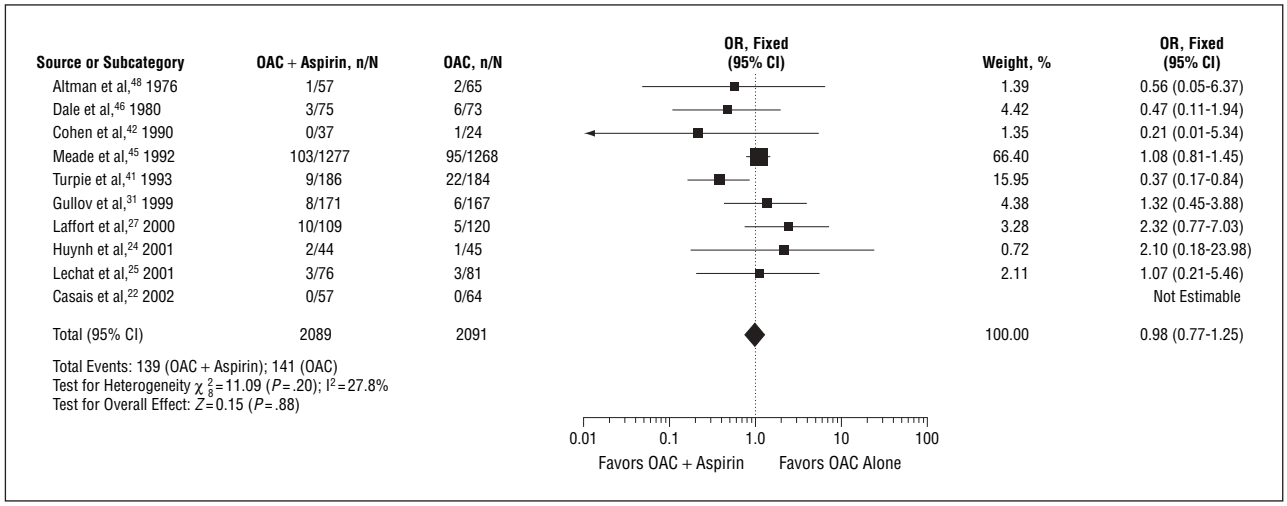

Figure 3. Risk for all-cause mortality in patients receiving aspirin + oral anticoagulant (OAC) therapy or OAC therapy alone. CI indicates confidence interval; n/N, number of patients at risk/total number of patients in treatment group; and OR, odds ratio.

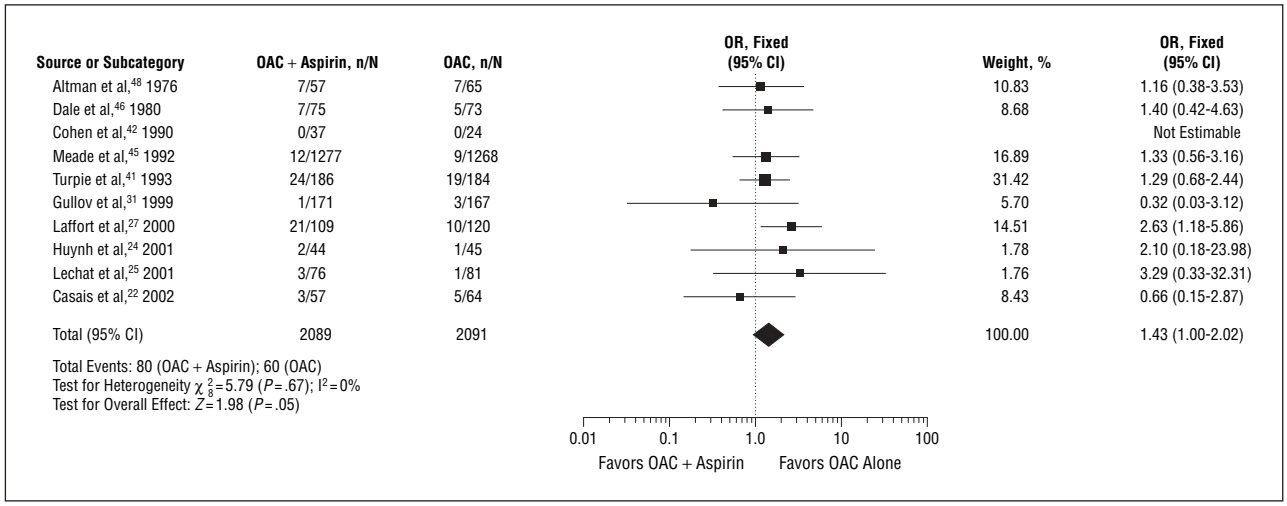

Figure 4. Risk for major bleeding in patients receiving aspirin + oral anticoagulant (OAC) therapy or OAC therapy alone. CI indicates confidence interval; n/N, number of patients at risk/total number of patients in treatment group; and OR, odds ratio.

by using a definition of major bleeding that would encompass the criteria used in various trials.[11]

The strengths of our meta-analysis include our use of a sensitivity analysis to assess the robustness of our findings in only high-quality studies, assessing for across-study heterogeneity for outcomes and, if necessary, accounting for this heterogeneity and assessing for publication bias. Our meta-analysis has advantages over other studies that compared aspirin-OAC and OAC therapy. Three prior meta-analyses assessed only patients with a mechanical heart valve[51,52] or CAD[53] and may have been underpowered to detect treatment effects, whereas we combined such patients. A fourth meta-analysis included studies in which the intensity of OAC therapy differed across treatment arms,[54] which may not permit a valid assessment of the additive effects of aspirin to OAC therapy. We only included studies in which patients in both treatment arms received the same OAC treatment regimen.

Our findings question the current practice of using combined aspirin-OAC therapy in patients with atrial fibrillation and concomitant CAD or in patients at high risk for stroke. This issue is likely to affect a large number of patients, since approximately 2.5 million people in North America have chronic atrial fibrillation, of whom 30% to 40% have concomitant CAD and 10% to 15% are considered at high risk for stroke.[3] Evidence for combined therapy in patients with a mechanical prosthetic heart valve is more compelling. In these patients, combination therapy is highly effective in reducing thromboembolic events.

In summary, our results suggest that, for patients receiving OAC therapy, the current practice of adding aspirin to their treatment should be considered carefully. The benefits in reducing thromboembolic events should be weighed against the increased risk of major bleeding. Large randomized trials are needed to assess the benefits and risks of these 2 treatment approaches in patients with both atrial fibrillation and CAD and high-risk patients with atrial fibrillation.

Accepted for Publication: September 20, 2006.

Correspondence: James D. Douketis, MD, FRCPC, St Joseph's Hospital, Room F-544, 50 Charlton Ave E, Hamilton, Ontario, Canada, L8N 4A6 (jdouket@mcmaster.ca).

Author Contributions: *Study concept and design:* Dentali and Douketis. *Acquisition of data:* Dentali, Lim, and Crowther. *Analysis and interpretation of data:* Dentali, Douketis, Lim, and Crowther. *Drafting of the manuscript:* Dentali, Douketis, and Crowther. *Critical revision of the manuscript for important intellectual content*: Dentali, Douketis, Lim, and Crowther. *Statistical analysis:* Dentali and Lim. *Obtained funding:* Douketis and Crowther. *Administrative, technical, and material support:* Crowther. *Study supervision:* Douketis and Crowther.

Financial Disclosure: None reported.

Funding/Support: Dr Crowther is a Career Investigator of the Heart and Stroke Foundation of Canada. Dr Lim holds a Canadian Institutes for Health Research RCT Mentoring Award.

Acknowledgment: We express gratitude to John Eikelboom, MD, and Lars Wallentin, MD, for their kind review of the manuscript.

REFERENCES

1. Salem DN, Stein PD, Al-Ahmad A, et al. Antithrombotic therapy in valvular heart disease-native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3)(suppl):457S-482S.
2. Douketis JD, Arneklev K, Goldhaber SZ, Spandorfer J, Halperin F, Horrow J. Comparison of bleeding in patients with nonvalvular atrial fibrillation treated with ximelagatran or warfarin: assessment of incidence, case fatality rate, time course, anatomic sites and risk factors for bleeding. *Arch Intern Med*. 2006;166:853-859.
3. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864-2870.
4. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:429S-456S.
5. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154:1449-1457.
6. Vink R, Kraaijenhagen RA, Hutten BA, et al. The optimal intensity of vitamin K antagonists in patients with mechanical heart valves: a meta-analysis. *J Am Coll Cardiol*. 2003;42:2042-2048.
7. Younossi ZM, Strum WB, Schatz RA, Teirstein PS, Cloutier DA, Spinks TJ. Effect of combined anticoagulation and low-dose aspirin treatment on upper gastrointestinal bleeding. *Dig Dis Sci*. 1997; 42:79-82.
8. Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke*. 2004;35:2362-2367.
9. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996; 17:1-12.
10. Schulz KF. Assessing allocation concealment and blinding in randomized controlled trials: why bother? *ACP J Club*. 2000;132:A11-A12.
11. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692-694.
12. McGinn T, Wyer PC, Newman TB, Keitz S, Leipzig R, For GG; Evidence-Based Medicine Teaching Tips Working Group. Tips for learners of evidence-based medicine: 3: measures of observer variability (kappa statistic). *CMAJ*. 2004;171:1369-1373.
13. Maclure M, Willett WC. Misinterpretation and misuse of the kappa statistic. *Am J Epidemiol*. 1987; 126:161-169.
14. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719-748.
15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
18. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med*. 2002;347:969-974.
19. Van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE; Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet*. 2002; 360:109-113.
20. Perez-Gomez F, Alegria E, Berjon J, et al; NASPEAF Investigators. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol*. 2004;44:1557-1566.
21. Rudnicka AR, Ashby D, Brennan P, Meade T. Thrombosis prevention trial: compliance with warfarin treatment and investigation of a retained effect. *Arch Intern Med*. 2003;163:1454-1460.
22. Casais P, Meschengieser SS, Sanchez Luceros AG, Bermejo EI, Lazzari MA. Effect of low-dose aspirin on the international normalized ratio variability in patients with mechanical heart valve prostheses. *Pathophysiol Haemost Thromb*. 2002; 32:155-157.
23. Knottenbelt C, Brennan PJ, Meade TW. Antithrombotic treatment and the incidence of angina pectoris. *Arch Intern Med*. 2002;162:881-886.

24. Huynh T, Theroux P, Bogaty P, et al. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. *Circulation*. 2001;103:3069-3074.
25. Lechat P, Lardoux H, Mallet A, et al. Anticoagulant (fluindione)-aspirin combination n patients with high-risk atrial fibrillation: a randomized trial (Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontane; FFAACS). *Cerebrovasc Dis*. 2001; 12:245-252.
26. Hurlen M, Smith P, Arnesen H. Effects of warfarin, aspirin and the two combined, on mortality and thromboembolic morbidity after myocardial infarction: the WARIS-II (Warfarin-Aspirin Reinfarction Study) design. *Scand Cardiovasc J*. 2000; 34:168-171.
27. Laffort P, Roudaut R, Roques X, et al. Early and long-term (one-year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St Jude medical prosthesis. *J Am Coll Cardiol*. 2000;35:739-746.
28. Lechat P, Lardoux H, Mallet A, et al; Investigateurs de FFAACS. Study of combined anticoagulant (fluindione)-aspirin therapy in patients with atrial fibrillation at high risk for thromboembolic complications: a randomized trial (FFAACS) [article in French]. *Therapie*. 2000;55:681-689.
29. Li-Saw-Hee FL, Blann AD, Lip GY. Effects of fixed low-dose warfarin, aspirin-warfarin combination therapy, and dose-adjusted warfarin on thrombogenesis in chronic atrial fibrillation. *Stroke*. 2000; 31:828-833.
30. Blackshear JL, Pearce LA, Hart RG, et al. Aortic plaque in atrial fibrillation: prevalence, predictors, and thromboembolic implications. *Stroke*. 1999;30:834-840.
31. Gullov AL, Gade Koefoed B, Petersen P. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation. *Arch Intern Med*. 1999;159: 1322-1328.
32. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet*. 1998; 351:233-241.
33. Gullov AL, Koefoed BG, Petersen P, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med*. 1998;158:1513-1521.
34. Hurlen M, Seljeflot I, Arnesen H. The effect of different antithrombotic regimens on platelet aggregation after myocardial infarction. *Scand Cardiovasc J*. 1998;32:233-237.
35. Fondevila CG, Meschengieser SS, Santareli MT, Aixala MT, Lazzari MA. Prevalence of anemia and occult blood losses in the long-term follow-up of cardiac mechanic valve patients treated with a combination of low-dose aspirin plus low-intensity acenocoumarin. *Clin Appl Thromb Hemost*. 1997;3:36-39.
36. Meschengieser SS, Fondevila CG, Frontroth J, Santareli MT, Lazzari MA. Low-intensity oral anticoagulation plus low-dose aspirin versus high-intensity oral anticoagulation alone: a randomized trial in patients with mechanical prosthetic heart valves. *J Thorac Cardiovasc Surg*. 1997;113: 910-916.
37. Richards M, Meade TW, Peart S, Brennan PJ, Mann AH. Is there any evidence for a protective effect of antithrombotic medication on cognitive function in men at risk of cardiovascular disease? some preliminary findings. *J Neurol Neurosurg Psychiatr*. 1997;62:269-272.
38. Voith L, Pfliegler G, Hegedus I, et al. Coumarin combined with low-dose acetylsalicylic acid in the prevention of thromboembolic complications in patients with mitral and aortic valve prostheses [article in Hungarian]. *Orv Hetil*. 1997;138:925-929.
39. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet*. 1996;348:633-638.
40. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;342:1255-1262.
41. Turpie AG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med*. 1993;329:524-529.
42. Cohen M, Adams PC, Bach M, et al. Usefulness of antithrombotic therapy in resting angina pectoris or non-Q-wave myocardial infarction in preventing death and myocardial infarction (a pilot study from the antithrombotic therapy in acute coronary syndromes study group). *Am J Cardiol*. 1990;66:1287-1292.
43. Dale J, Myhre E. Prevention of arterial embolism by acetylsalicyclic acid and anticoagulants in patients with heart valve prosthesis [article in Norwegian]. *Tidsskr Nor Laegeforen*. 1976;96: 1483-1485.
44. Chesebro JH, Fuster V, Elveback LR, et al. Trial of combined warfarin plus dipyridamole or aspirin therapy in prosthetic heart valve replacement: danger of aspirin compared with dipyridamole. *Am J Cardiol*. 1983;51:1537-1541.
45. Meade TW, Roderick PJ, Brennan PJ, Wilkes HC, Kelleher CC. Extra-cranial bleeding and other symptoms due to low dose aspirin and low intensity oral anticoagulation. *Thromb Haemost*. 1992; 68:1-6.
46. Dale J, Myhre E, Loew D. Bleeding during acetylsalicylic acid and anticoagulant therapy in patients with reduced platelet reactivity after aortic valve replacement. *Am Heart J*. 1980;99:746-752.
47. Dale J, Myhre E, Storstein O, et al. Prevention of arterial thromboembolism with acetylsalicylic acid. *Am Heart J*. 1977;94:101-111.
48. Altman R, Boullon F, Rouvier J, et al. Aspirin and prophylaxis of thromboembolic complications in patients with substitute heart valves. *J Thorac Cardiovasc Surg*. 1976;72:127-129.
49. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345: 494-502.
50. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study, 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996; 143:1-13.
51. Cappelleri JC, Fiore LD, Brophy MT, Deykin D, Lau J. Efficacy and safety of combined anticoagulant and antiplatelet therapy versus anticoagulant monotherapy after mechanical heart-valve replacement: a meta-analysis. *Am Heart J*. 1995; 130:547-552.
52. Massel D, Little SH. Risks and benefits of adding anti-platelet therapy to warfarin among patients with prosthetic heart valves: a meta-analysis. *J Am Coll Cardiol*. 2001;37:569-578.
53. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA*. 1999;282:2058-2067.
54. Larson RJ, Fisher ES. Should aspirin be continued in patients started on warfarin? *J Gen Intern Med*. 2004;19:879-886.