REVIEW

Should Aspirin be Continued in Patients Started on Warfarin?

A Systematic Review and Meta-analysis

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BACKGROUND AND OBJECTIVE: Clinicians frequently face the decision of whether to continue aspirin when starting patients on warfarin. We performed a meta-analysis to characterize the tradeoffs involved in this common clinical dilemma.

DATA SOURCES: Multiple computerized databases (1966 to 2003), reference lists of relevant articles, conference proceedings, and queries of primary authors.

STUDY SELECTION: Randomized trials comparing warfarin plus aspirin versus warfarin alone. Studies with target international normalized ratios (INRs) <2 were excluded.

DATA EXTRACTION: Two reviewers independently extracted baseline data and major outcomes: rates of thromboembolism, hemorrhage, and all-cause mortality.

DATA SYNTHESIS: Nine studies met the inclusion criteria. Of the five that enrolled patients with mechanical heart valves, four used the same target INR in both groups, while one used a reduced target INR for the warfarin plus aspirin group. Pooling the results of the first four studies demonstrated that combination of warfarin plus aspirin significantly decreased thromboembolic events (relative risk [RR], 0.33; 95% confidence interval [CI], 0.19 to 0.58), increased major bleeding (RR, 1.58; 95% CI, 1.02 to 2.44), and decreased all-cause mortality (RR, 0.43; 95% CI, 0.23 to 0.81) compared to warfarin alone. The one valve trial using a reduced INR in the warfarin plus aspirin group reported no difference in thromboembolic outcomes but found decreased major bleeding and a significant mortality benefit with combination therapy. Of the remaining trials, three evaluated a warfarin indication not routinely used in the United States (post-myocardial infarction), and the only trial that considered atrial fibrillation was terminated early due to inadequate enrollment.

CONCLUSIONS: For mechanical heart valve patients, the benefits of continuing aspirin when starting warfarin therapy are clear. For other routine warfarin indications, there are not adequate data to guide this common clinical decision.

KEY WORDS: aspirin; warfarin; thromboembolism; hemorrhage; mortality.

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Because of data demonstrating a lower risk of myocardial infarction (MI) and stroke,^{1–3} the number of Americans taking daily aspirin is approaching 23 million.⁴ At the same time, clinicians are being encouraged to use warfarin more frequently in response to growing evidence of benefit in multiple conditions.^{5–11} As a consequence, warfarin is increasingly recommended in patients who are already on aspirin, raising the question of whether or not to continue the aspirin once anticoagulation is initiated.

Reasonable clinical arguments have been made for both approaches. On the one hand, proponents of continuing aspirin with warfarin therapy have hypothesized additive antithrombotic protection when both platelet function and coagulation factor activity are suppressed. On the other hand, those warning against dual therapy have cautioned that the potential for increased bleeding would be unacceptably high, surely outweighing any theoretical benefits.

In order to describe these tradeoffs quantitatively, we performed a systematic review and meta-analysis of any randomized trials comparing adjusted-dose warfarin plus aspirin versus adjusted-dose warfarin alone. We aimed to characterize the efficacy and safety of the two treatment strategies by comparing thromboembolic, bleeding, and mortality outcomes in conditions in which these drugs might be used concomitantly.

METHODS

Data Sources

We used a Cochrane Optimized Medline Search Strategy (see Appendix) to locate randomized, controlled trials involving warfarin (or comparable oral vitamin K antagonists) and aspirin published in English language journals between 1966 and October 2003. Other large databases including the American College of Physicians Journal Club (ACP), the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Database of Abstracts of Reviews of Effectiveness

Received from the VA Outcomes Group (R.J.L., E.S.F.), Department of Veteran Affairs Medical Center, White River Junction, Vt; and Center for the Evaluative Clinical Sciences (R.J.L., E.S.F.), Dartmouth Medical School, Hanover, NH.

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(DARE) were searched using the same strategy. We manually reviewed the bibliographies of selected and related articles for any pertinent references overlooked by the computerized searches and explored national and international conference proceedings for abstracts of relevant work not yet published.

Study Selection

References identified by the computerized searches were imported into a computer database for review. Full text articles were obtained of references that either appeared to meet the inclusion criteria or could not be excluded by abstract and title review alone. Studies were ultimately selected for the synthesis if they 1) described an explicitly randomized trial that compared adjusted-dose warfarin plus aspirin versus adjusted-dose warfarin alone; 2) targeted all anticoagulation to an international normalized ratio (INR) goal ≥ 2 (two trials predating the INR system^{12,13} were judged to reflect comparable anticoagulation goals); 3) reported event rates for at least one of the outcomes of interest (thromboembolism, hemorrhage, and all-cause mortality); and 4) had a minimum of 3 months of follow-up. Blinding of treatment and outcome assessments was tracked but not utilized as an inclusion/exclusion criterion. Reviewers were not blinded to journal titles, author names, or institutional affiliations.

Data Extraction

For each study selected for the synthesis two reviewers independently extracted the data of interest. Items recorded for each trial included authors' names, year of publication, period of trial conduction, patient characteristics, study design, number enrolled, treatment arms included, target INRs, mean INRs achieved, aspirin dosages, rates of reported outcomes, and duration of follow-up. If important pieces of data could not be located in a published report, efforts were made to contact the corresponding authors in order to obtain the missing details. Information was entered into a data collection spreadsheet by each reviewer and then compared for consistency. Disagreements were resolved via discussion.

Data Synthesis

Statistical calculations were performed using Revman software.¹⁴ For each trial, the relative risk and 95% confidence interval of warfarin plus aspirin versus warfarin alone were calculated for each endpoint of interest. For warfarin indications with more than one trial assessing comparable treatment regimens, the χ^2 test for heterogeneity was used to assess the appropriateness of pooling the individual study results. If a grouping of trial results was found to be heterogeneous (using a P value cutoff of .10), the χ^2 test of heterogeneity was recalculated excluding each member trial in sequence to determine the largest grouping of homogeneous trials. Where appropriate, final pooled risk estimates

FIGURE 1. Trial identification and selection process. RCT, randomized, controlled trial.

by warfarin indication were calculated using a random effects model with a P value $< .05$ being considered significant. Absolute risk reductions for each endpoint by warfarin indication were manually calculated by subtracting the pooled event rates for each treatment group from the pooled event rates for each corresponding control group.

RESULTS

Study Selection

Eight hundred twenty-five potential articles were initially located by the computerized searches. As shown in Figure 1, the majority of exclusions were made due to lack of randomization or missing treatment arms. Manual reference review led to the identification of one additional randomized trial.¹³ Ultimately, the searches resulted in a collection of nine qualifying trials,^{12,13,15–22} which together addressed three warfarin indications (Table 1).

Table 1. Number of Qualifying Trials by Warfarin Indication

Warfarin Indication	Number of Qualifying Trials
Systemic Embolism, prevention	
Atrial Fibrillation	1
Tissue Heart Valves	0
Valvular Heart Disease	0
Acute Myocardial Infarction*	0
Venous Thrombosis, prevention	0
Venous Thrombosis, treatment	0
Pulmonary Embolism, treatment	0
Mechanical Prosthetic Valves	5
Acute Myocardial Infarction, secondary prevention†	3

Adapted from the Sixth ACCP Consensus Conference on Antithrombotic Therapy.²³

* To prevent systemic embolism (i.e., from left ventricular mural thrombus or in patients with high-risk anterior wall motion abnormalities).⁴¹

† Though not a commonly used indication in the United States, recent work from Europe²⁰ has rekindled discussion regarding the use of warfarin for secondary prevention after myocardial infarction.

Study Characteristics

A summary of the trials included in the synthesis is shown in Table 2. Five involved mechanical heart valve recipients,^{12,13,15-18} three were performed in post-myocardial infarction (post-MI) subjects,¹⁹⁻²¹ and one had been conducted in atrial fibrillation patients at high risk for thromboembolic disease.²² For each warfarin indication, the trials were further stratified to separate those that evaluated a single warfarin regimen with and without aspirin (single intervention)^{12,13,15-17,19,22} from those that compared moderate-intensity warfarin plus aspirin versus higher-intensity warfarin alone (double intervention).^{18,20,21} This division permitted assessment of the trials that specifically isolated the effect of aspirin separately from those that varied both the presence of aspirin and the intensity of the anticoagulation.

Mechanical Heart Valves

Thromboembolic Events. Thromboembolic events were defined similarly in all five valve trials and typically included valve thromboses, systemic emboli, cerebrovascular emboli, and MIs occurring in the absence of significant coronary artery lesions. Transient ischemic attacks were included in four of the five trials.^{12,13,15,18} As shown in Table 3, thromboembolic event rates were lower in the combination therapy groups in all four of the single-intervention trials^{12,13,15-17} (pooled relative risk [RR], 0.33; 95% confidence interval [CI], 0.19 to 0.58; absolute risk reduction [ARR], 7.8%; number needed to treat [NNT], 13). For the double-intervention trial,¹⁸ thromboembolic event rates were low in both groups and essentially equivalent.

Major Bleeding. Major bleeding typically included episodes that led to a drop in hemoglobin of >2 g/dL, required hospitalization or transfusion of blood products, or resulted in death. Again shown in Table 3, major bleeding events were increased or equivalent with warfarin plus aspirin in all three of the single-intervention trials reporting this outcome^{13,15,16} (pooled RR, 1.58; 95% CI, 1.02 to 2.44; ARR, -5%; NNH, 20). Conversely, the double-intervention trial¹⁸ found fewer bleeding events in the combination therapy group.

All-cause Mortality. Because the test of heterogeneity was significant for the combined group ($P = .07$), we pooled the single-intervention all-cause mortality findings both before and after excluding the Laffort results (the only trial finding increased mortality with combination therapy).¹⁵ Using the data from all four trials^{12,13,15,16} resulted in a nonsignificant 28% reduction with combination therapy (pooled RR, 0.72; 95% CI, 0.29 to 1.83; ARR, 2.5%; NNT, 40). Removing the outlying trial resulted in a statistically significant 57% decreased risk (pooled RR, 0.43; 95% CI, 0.23 to 0.81; ARR, 5.2%; NNT, 19). A similar 59% mortality reduction with combination therapy was seen in the double-intervention trial.¹⁸

Post-myocardial Infarction Trials

Subsequent Myocardial Infarction. The post-MI trials tracked subsequent cardiac events defined by clinical, electrocardiogram, and laboratory parameters. As shown in Table 4, subsequent nonfatal MI rates were decreased with combination therapy in all three trials but none achieved statistical significance. Pooling the two trials evaluating a double intervention^{20,21} resulted in a 23% nonsignificant reduction in subsequent MI risk (pooled RR, 0.77; 95% CI, 0.58 to 1.03; ARR, 1.3%; NNT, 77).

Major Bleeding. Major bleeding was again defined to include episodes that led to a drop in hemoglobin of >2 g/dL, required hospitalization or transfusion of blood products, or resulted in death. As shown in Table 4, the major bleeding outcomes were mixed. The single trial with identical INR targets in both treatment groups (single intervention)¹⁹ reported a nonsignificant 3-fold increased risk of major bleeding for the combination therapy group. The two double-intervention trials in which the target INRs were lower in the warfarin plus aspirin groups^{20,21} suggested no clear difference in bleeding rates between the two treatment strategies (pooled RR, 1.14; 95% CI, 0.47 to 2.73).

All-cause Mortality. Two trials^{19,21} found nonsignificant increases in all-cause mortality with combination therapy whereas the remaining trial²⁰ showed no mortality difference. Combining the double-intervention trials^{20,21} revealed a pooled risk of 1.20 (95% CI, 0.62 to 2.32).

Atrial Fibrillation Trials

Thromboembolic Events, Major Bleeding, and All-cause Mortality. The single atrial fibrillation trial²² evaluated 157 elderly subjects at high risk for thromboembolic events (average age approximately 74 years). Thromboembolic events included ischemic and hemorrhagic cerebrovascular accidents; MIs meeting clinical, electrocardiogram, and lab criteria; and systemic arterial emboli of cardiac origin affecting mesenteric, renal, splenic, or limb arteries. Major bleeding events included those requiring specific treatment such as transfusions or hospitalization. Though the trial was not adequately powered due to slow enrollment and subsequent early termination, thromboembolic and major bleeding rates were higher in the combined therapy group (RR, 2.13; 95% CI, 0.20 to 23.03 for both outcomes) and mortality was essentially equivalent (RR, 1.07; 95% CI, 0.22 to 5.12) (Table 5). The wide confidence intervals however, caution against drawing any major conclusions from the results.

DISCUSSION

Despite the growing prevalence of aspirin use among patients starting warfarin, five of the nine randomized trials that specifically assessed the benefits and harms of

Table 2. Characteristics of Randomized, Controlled Trials Comparing Adjusted-dose Warfarin plus Aspirin to Adjusted-dose Warfarin Alone

Author (Reference)	Year	Study Population	N	Age (mean yrs)	Sex (% male)	Warfarin* Plus Aspirin INR Target (mean)	Aspirin Dose	Warfarin*-only INR Target (mean)	Blinding	Duration F-up (mean)
Mechanical Heart Valve Trials										
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>										
Laffort (15)	2000	Mechanical Mitral (60%) and Aortic + Mitral (40%) Valve Patients	229	63	50	2.5 to 3.5 (3.04)	200 mg qd	2.5 to 3.5 (3.03)	open-label	1 yr
Turpie (16)	1993	Mechanical [†] Aortic (46%), Mitral (44%) and Multiple (10%) Valve Patients	370	58	51	3.0 to 4.5 (3.0)	100 mg qd	3.0 to 4.5 (3.1)	double-blinded aspirin, open-label warfarin	2.5 yrs
Dale (12,17)	1977	Mechanical Aortic (100%) Valve Patients	148	51 [‡]	75	TT 10% nl	500 mg bid	TT 10% nl	double-blinded aspirin, open-label warfarin	2 yrs
Altman (13)	1976	Mechanical Aortic (26%) and Mitral (74%) Valve Patients	122	NR	75	PT 1.8 to 2.3 × nl	500 mg qd	PT 1.8 to 2.3 × nl	open-label	2 yrs
<i>Double Intervention Trials (Comparing moderate intensity warfarin plus aspirin versus higher intensity warfarin alone)</i>										
Meschengieser (18)	1997	Mechanical Aortic (66%), Mitral (29%) and Aortic + Mitral (4%) Valve Patients	503	53 (median)	58	2.5 to 3.5 (3.11)	100 mg qd	3.5 to 4.5 (3.98)	open-label	2 yrs (median)
Post-Myocardial Infarction Trials										
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>										
Huynh (19)	2001	Post-Myocardial Infarction (100% NQW) and Unstable Angina Patients with h/o CABG	89 [§]	67	79	2.0 to 2.5 (NR)	80 mg qd	2.0 to 2.5 (NR)	double-blinded W and A	1 yr
<i>Double Intervention Trials (Comparing moderate intensity warfarin plus aspirin versus higher intensity warfarin alone)</i>										
Hurlen (20) WARIS-2	2002	Post-Myocardial Infarction (41% NQW) Patients	2424 [§]	60	77	2.0 to 2.5 (2.2)	75 mg qd	2.8 to 4.2 (2.8)	open label	4 yrs
Van Es (21) ASPECT-2	2002	Post-Myocardial Infarction (40.6% NQW, 46.7% QW) and Unstable Angina (12.6%) Patients	647 [§]	62	75	2.0 to 2.5 (2.4)	80 mg qd	3.0 to 4.0 (3.2)	open-label	1 yr
Atrial Fibrillation Trials										
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>										
Lechat (22)	2001	High-Risk [¶] Non-Valvular Atrial Fibrillation Patients	157	74	48	2.0 to 2.6 (NR)	100 mg qd	2.0 to 2.6 (NR)	double-blinded aspirin	0.84 yr

* Specific oral anticoagulant: warfarin,^{16,19,20} acenocoumarin,¹³ phenprocoumon or acenocoumarol,²¹ fluindione,²² not reported.^{12,15,17,18}

[†] Twenty-four percent of patients had tissue valves with atrial fibrillation or h/o thromboembolism.

[‡] Age at time of AVR >2 years (mean 42 months) prior to study entry.

[§] All three post-MI trials had a third "aspirin-only" arm; overall numbers enrolled were 135,¹⁹ 3630,²⁰ and 993.²¹

^{||} Trial was stopped early due to slow enrollment.

[¶] h/o thromboembolic event OR age >65 and h/o HTN (>160/90), recent CHF episode, or EF <40%.

N, number enrolled; INR, international normalized ratio; TT, thrombotest; PT, prothrombin time; nl, normal; CHF, congestive heart failure; h/o, history of; AVR, aortic valve repair; EF, ejection fraction; CABG, coronary artery bypass grafting; qd, daily; NQW, non-Q-wave; QW, Q-wave.

Table 3. Results of Mechanical Heart Valve Trials Comparing Warfarin Plus Aspirin to Warfarin Alone

Study	Duration (mean yrs)	Warfarin plus asa n/N	Warfarin alone n/N	RR (95%CI Random)	RR (95%CI Random)	ARR
Thromboembolic Events						
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>						
Laffort	1	5 / 109 (4.6%)	12 / 120 (10.0%)	0.46 [0.17,1.26]		
Turpie	2.5	5 / 186 (2.7%)	13 / 184 (7.1%)	0.38 [0.14,1.05]		
Dale	2	2 / 75 (2.7%)	12 / 73 (16.4%)	0.16 [0.04,0.70]		
Altman	2	3 / 57 (5.3%)	13 / 65 (20.0%)	0.26 [0.08,0.88]		
Total *		15 / 427 (3.5%)	50 / 442 (11.3%)	0.33 [0.19,0.58]		7.8% (NNT 13)
<i>Double Intervention Trials (Comparing moderate intensity warfarin plus aspirin versus higher intensity warfarin alone)</i>						
Meschengieser	2	7 / 258 (2.7%)	7 / 245 (2.8%)	0.95 [0.34,2.67]		
Major Bleeding						
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>						
Laffort	1	21 / 109 (19.3%)	10 / 120 (8.3%)	2.31 [1.14,4.69]		
Turpie	2.5	24 / 186 (12.9%)	19 / 184 (10.3%)	1.25 [0.71,2.20]		
Altman	2	1 / 57 (1.8%)	1 / 65 (1.5%)	1.14 [0.07,17.82]		
Total **		46 / 352 (13.1%)	30 / 369 (8.1%)	1.58 [1.02,2.44]		-5.0% (NNH 20)
<i>Double Intervention Trials (Comparing moderate intensity warfarin plus aspirin versus higher intensity warfarin alone)</i>						
Meschengieser	2	6 / 258 (2.3%)	11 / 245 (4.5%)	0.52 [0.19,1.38]		
All-Cause Mortality						
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>						
Laffort	1	10 / 109 (9.2%)	5 / 120 (4.2%)	2.20 [0.78,6.24]		
Turpie	2.5	9 / 186 (4.8%)	22 / 184 (12.0%)	0.40 [0.19,0.86]		
Dale	2	3 / 75 (4.0%)	6 / 73 (8.2%)	0.49 [0.13,1.87]		
Altman	2	1 / 57 (1.8%)	2 / 65 (3.1%)	0.57 [0.05,6.12]		
Total ***		23 / 427 (5.4%)	35 / 442 (7.9%)	0.72 [0.29,1.83]		2.5% (NNT 40)
<i>Excluding Laffort Trial</i>						
Total ****		13 / 318 (4.1%)	30 / 322 (9.3%)	0.43 [0.23,0.81]		5.2% (NNT 19)
<i>Double Intervention Trials (Comparing moderate intensity warfarin plus aspirin versus higher intensity warfarin alone)</i>						
Meschengieser	2	9 / 258 (3.5%)	21 / 245 (8.6%)	0.41 [0.19,0.87]		

n=number of subjects experiencing event, N=number of subjects in treatment arm, RR=Relative Risk, VV+A=Warfarin plus aspirin, VV=Warfarin, CI=Confidence Interval, ARR=Absolute Risk Reduction, NNT=Number Needed to Treat, NNH=Number Needed to Harm

*Test for heterogeneity chi-square=1.54, p=0.67

**Test for heterogeneity chi-square=1.83, p=0.40

***Test for heterogeneity chi-square=6.99, p=0.072

****Test for heterogeneity chi-square=0.11, p=0.95

combination warfarin plus aspirin therapy were restricted to patients with mechanical heart valves. Three involved an indication rarely used in the United States (routine post-MI) and only one focused on patients with the most common chronic indication, atrial fibrillation. None included patients with any of the other ACCP Committee on Antithrombotic Therapy-sanctioned indications (Table 1).²³ Nonetheless, some inferences can be drawn from the limited data available. Mechanical heart valve patients have a clear overall benefit from combining aspirin with warfarin therapy. Post-MI patients probably have a reduced risk of thromboembolic events but appear to have no decrease (and perhaps an increase) in overall mortality.

Finally, because the atrial fibrillation trial was terminated early, there are no data from which to draw conclusions regarding this increasingly prevalent indication.

While a number of trials, reviews, and meta-analyses have evaluated varying combinations of warfarin and aspirin,²⁴⁻³⁴ few have addressed the specific clinical question—"Should aspirin be continued in patients started on warfarin?" Instead, previous work has tended to focus on two other aspects of antithrombotic therapy, "What is the benefit of adding warfarin to aspirin?" (i.e., warfarin plus aspirin versus aspirin alone) and, "Can the intensity of warfarin be reduced if combined with aspirin?" (i.e., fixed-dose/low-intensity warfarin (INR <2) plus aspirin versus

Table 4. Results of Post-Myocardial Infarction Trials Comparing Warfarin Plus Aspirin to Warfarin Alone

Study	Duration (mean yrs)	Warfarin plus asa n/N	Warfarin alone n/N	RR (95%CI Random)	RR (95%CI Random)	ARR
Subsequent Myocardial Infarction Events						
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>						
Huynh	1	3 / 44 (6.8%)	4 / 45 (8.9%)	0.77 [0.18,3.23]		
<i>Double Intervention Trials (Comparing moderate intensity warfarin plus aspirin versus higher intensity warfarin alone)</i>						
Hurlen	4	69 / 1208 (5.7%)	90 / 1216 (7.4%)	0.77 [0.57,1.05]		
Van Es	1	10 / 332 (3.0%)	13 / 335 (3.9%)	0.78 [0.35,1.75]		
Total*		79 / 1540 (5.1%)	103 / 1551 (6.6%)	0.77 [0.58,1.03]		1.3% (NNT 77)
Major Bleeding						
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>						
Huynh	1	3 / 44 (6.8%)	1 / 45 (2.2%)	3.07 [0.33,28.38]		
<i>Double Intervention Trials (Comparing moderate intensity warfarin plus aspirin versus higher intensity warfarin alone)</i>						
Hurlen	4	28 / 1208 (2.3%)	33 / 1216 (2.7%)	0.85 [0.52,1.40]		
Van Es	1	7 / 332 (2.1%)	3 / 325 (0.9%)	2.28 [0.60,8.76]		
Total**		35 / 1540 (2.3%)	36 / 1541 (2.3%)	1.14 [0.47,2.73]		N/A
All-Cause Mortality						
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>						
Huynh	1	2 / 44 (4.5%)	1 / 45 (2.2%)	2.05 [0.19,21.76]		
<i>Double Intervention Trials (Comparing moderate intensity warfarin plus aspirin versus higher intensity warfarin alone)</i>						
Hurlen	4	95 / 1208 (7.9%)	96 / 1216 (7.9%)	1.00 [0.76,1.31]		
Van Es	1	9 / 332 (2.7%)	4 / 325 (1.2%)	2.20 [0.69,7.08]		
Total***		104 / 1540 (6.8%)	100 / 1541 (6.5%)	1.20 [0.62,2.32]		-0.3% (NNH 333)

n=number of subjects experiencing event, N=number of subjects in treatment arm, RR=Relative Risk, CI=Confidence Interval, ARR=Absolute Risk Reduction, NNT=Number Needed to Treat to benefit/harm one
N/A=not applicable, W+A=Warfarin plus aspirin, W=Warfarin

* Test for heterogeneity chi-square=0.00 p=0.99

** Test for heterogeneity chi-square=1.81 p=0.18

*** Test for heterogeneity chi-square=1.68 p=0.19

adjusted-dose warfarin [INR ≥ 2] alone). Though the efficacy and safety of combining warfarin and aspirin was reviewed in 1998,³⁵ in its effort to be comprehensive the synthesis mixed trials addressing all three questions. Conversely, when previous investigators have focused specifically on questions comparable to our own,³⁶⁻³⁹ their reviews have been confined to mechanical heart valve trials. To our knowledge, our report is the first to focus on the tradeoffs of concomitant aspirin use in multiple adjusted-dose warfarin indications.

Nonetheless, our study is clearly limited by the small number of trials that fulfilled the inclusion criteria and the narrow scope of warfarin indications covered by the few qualifying trials. We did not have access to Excerpta Medica database but have no reason to believe that it contains additional relevant trials not detected by our present search strategy. While the initial study screening was performed by a single reviewer, our well-defined inclusion criteria made study selection straightforward and articles that presented any question were reviewed by both investigators prior to exclusion. Certainly the requirement that all warfarin be

dose adjusted to INRs ≥ 2.0 eliminated many high-quality studies from the synthesis. Even so, because these same studies have shown INRs < 2.0 to be inferior, thereby directing the current recommendations targeting INRs ≥ 2.0 for every standard warfarin indication,²³ the inclusion criterion was necessary in order to target the clinically relevant question.

Additional limitations might stem from the poor availability of information to assess study quality, and the variation in treatment regimens used in the studies. Although we stratified the trials by "single" and "double" intervention status in order to assess the effects of the differing study designs separately, even among the single-intervention trials the target INRs ranged from as low as 2.0 to 2.5 to as high as 3.0 to 4.5. Similarly, the aspirin doses ranged from 75 to 1,000 mg per day. Despite the diversity, however, no obvious relationship between the study outcomes and the INR ranges or aspirin doses was detected. In fact, the highest bleeding rates were seen in a trial using both a conservative target INR range and a modest aspirin dose.¹⁵

Admittedly, the primary aim of most trials evaluating warfarin and aspirin combinations has been to assess

Table 5. Results of Atrial Fibrillation Trials Comparing Warfarin Plus Aspirin to Warfarin Alone*

Study	Duration (mean yrs)	Warfarin plus asa n/N	Warfarin alone n/N	RR (95%CI Random)	RR (95%CI Random)
Thromboembolic Events					
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>					
Lechat	1	2 / 76 (2.6%)	1 / 81 (1.2%)	2.13 [0.20,23.03]	
Major Bleeding					
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>					
Lechat	1	2 / 76 (2.6%)	1 / 81 (1.2%)	2.13 [0.20,23.03]	
All-Cause Mortality					
<i>Single Intervention Trials (Comparing a single warfarin regimen with and without aspirin)</i>					
Lechat	1	3 / 76 (3.9%)	3 / 81 (3.7%)	1.07 [0.22,5.12]	

n=number of subjects experiencing event, N=number of subjects in treatment arm, RR=Relative Risk, W+A=Warfarin* plus aspirin, W=Warfarin*, CI=Confidence Interval

*The "warfarin-like" oral vitamin K antagonist used in this trial was fluindione

whether the addition of aspirin provides added protection in terms of the thrombosis risk for which the warfarin is indicated, without leading to excessive bleeding. While this question is different from asking whether it is safe to continue prophylactic aspirin (for prevention of MI and stroke) in patients requiring warfarin for alternative diagnoses (i.e., deep venous thrombosis, pulmonary embolism, stroke prevention in atrial fibrillation or following valve replacement, etc.), trials designed to address these questions would be virtually indistinguishable. Though the inclusion criteria might require that subjects also meet defined criteria for prophylactic aspirin (i.e., prior heart attack or >10% 10-year risk of cardiovascular disease), such trials would compare warfarin plus aspirin to warfarin alone and the outcomes of interest would include thromboembolic events, bleeding, and all-cause mortality.

Because our review was specifically intended to address aspirin use in patients requiring warfarin, we considered carefully whether the post-MI trials were appropriate for the synthesis. Indeed in the United States, aspirin has been the traditional first-line prevention therapy following acute MI, whereas warfarin has been reserved for patients intolerant to aspirin, with left ventricular mural thrombus or high-risk anterior wall motion abnormalities, or with recurrent thrombotic events on aspirin alone. With the publication of the most recent post-MI trial,²⁰ however, it appears that our question may be relevant for this patient group as well. Because both the warfarin plus aspirin and warfarin-only groups had fewer thromboembolic events compared to the aspirin-only group, attention is now being given to whether anticoagulation-based secondary prevention therapies should be more aggressively considered in this country. For those clinicians and patients who choose to focus on minimizing thromboembolic risk, these results suggest that combined warfarin plus aspirin therapy offers the best protection. On the other hand, for those who choose to focus on the broader overall mortality outcomes,

the findings suggest that neither the addition of nor substitution with warfarin offers a mortality advantage over aspirin alone.

In the end, we are left with a striking lack of evidence regarding aspirin use in the most common warfarin indications. Unfortunately, the variations in outcomes among the conditions we were able to evaluate suggest that extrapolating from one warfarin indication to another may not be appropriate. Nonetheless, with over 2 million people in the United States affected by atrial fibrillation and approaching 200,000 new cases per year,⁴⁰ the issues raised here will only become more relevant. For now, decisions about the use of aspirin in most patients receiving warfarin will need to be individualized in the absence of adequate data.

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APPENDIX

Cochrane Optimized Medline Search Strategy for Identifying Randomized, Controlled Trials

Database: MEDLINE <1966 to October Week 5 2003>

Search Strategy:

1. randomized controlled trial.pt.
 2. controlled clinical trial.pt.
 3. randomized controlled trials.sh.
 4. random allocation.sh.
 5. double-blind method.sh.
 6. single-blind method.sh.
 7. or/1 to 6
 8. (animal not human).sh.
 9. 7 not 8
 10. clinical trial.pt.
 11. exp clinical trials/
 12. (clin\$ adj25 trial\$).ti,ab.
 13. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
 14. placebos.sh.
 15. placebo\$.ti,ab.
 16. random\$.ti,ab.
 17. research design.sh.
 18. or/10 to 17
 19. 18 not 8
 20. 19 not 9
 21. comparative study.sh.
 22. exp evaluation studies/
 23. follow-up studies.sh.
 24. prospective studies.sh.
 25. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
 26. or/21 to 25
 27. 26 not 8
 28. 27 not (9 or 20)
 29. 9 or 20 or 28
 30. ((warfarin or coumadin) and aspirin).mp.
 31. 29 and 30
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