

Aspirin for the Prevention of Recurrent Venous Thromboembolism: The INSPIRE Collaboration

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Circulation. published online August 25, 2014;

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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**Aspirin for the Prevention of Recurrent Venous Thromboembolism:
The INSPIRE Collaboration**

Running title: *Simes et al.; INSPIRE: aspirin for recurrent VTE*

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Journal Subject Codes: Thrombosis:[92] Platelets, Thrombosis:[173] Deep vein thrombosis

Abstract

Background—In patients with a first unprovoked venous thromboembolism (VTE) the risk of recurrent VTE remains high after anticoagulant treatment is discontinued. The WARFASA and ASPIRE trials showed that aspirin reduces this risk, but they were not individually powered to detect treatment effects for particular outcomes or subgroups.

Methods and Results—An individual-patient-data analysis of these trials was planned, before their results were known, to assess the effect of aspirin versus placebo on recurrent VTE, major vascular events (recurrent VTE, MI, stroke and CVD death) and bleeding, overall and within predefined subgroups. The primary analysis, for VTE, was by intention to treat using time-to-event data. Of 1224 patients, 193 had recurrent VTE over 30.4 months' median follow-up. Aspirin reduced recurrent VTE (7.5%/year vs 5.1%/year; hazard ratio (HR), 0.68; 95% CI, 0.51–0.90; $P=0.008$), including both deep-vein thrombosis (HR, 0.66; 95% CI, 0.47–0.92; $P=0.01$) and pulmonary embolism (HR, 0.66; 95% CI, 0.41–1.06; $P=0.08$). Aspirin reduced major vascular events (8.7%/year vs 5.7%/year; HR, 0.66; 95% CI, 0.50–0.86; $P=0.002$). The major bleeding rate was low (0.4%/year for placebo and 0.5%/year for aspirin). After adjustment for treatment adherence, recurrent VTE was reduced by 42% (HR, 0.58; 95% CI, 0.40–0.85; $P=0.005$). Prespecified subgroup analyses indicate similar relative, but larger absolute, risk reductions in men and older patients

Conclusions—Aspirin after anticoagulant treatment reduces the overall risk of recurrence by more than a third in a broad cross-section of patients with a first unprovoked VTE, without significantly increasing the risk of bleeding.

Clinical Trial Registration Information—National Health and Medical Research Council (Australia) (ACTRN12611000684921 at www.anzctr.org.au).

Key words: venous thrombosis, aspirin, anticoagulation, embolism, prevention

Introduction

Patients with unprovoked venous thromboembolism (VTE) remain at high risk of recurrence following discontinuation of vitamin K antagonist therapy, with about a 10% risk within the first year and 5% per year thereafter.¹⁻⁶ Extending treatment with vitamin K antagonists reduces the risk of recurrence while treatment continues,¹⁻⁷ but is associated with an increased risk of bleeding and the inconvenience of laboratory monitoring and dose adjustment.⁸

Several studies have evaluated the efficacy of new oral anticoagulants for the prevention of recurrent VTE as part of initial or extended treatment.⁹⁻¹⁴ They have been shown to be effective alternatives to warfarin, but still carry a risk of bleeding and are expensive. Aspirin treatment, as a low cost and relatively safe means of preventing further events in this clinical setting, has been recently evaluated in the WARFASA and ASPIRE trials.^{15,16} The trials showed that aspirin reduces the risk of recurrent VTE but they were not individually powered to detect moderate treatment effects for particular outcomes or subgroups.

A combined patient-level analysis of WARFASA and ASPIRE was planned and a protocol for this project was developed before unblinding of the results of either trial (ACTRN12611000684921). The purpose of the INSPIRE analysis was to more accurately estimate the effects of aspirin treatment: overall, on individual outcomes and in prespecified subgroups of patients.

Methods

Study protocols

The ASPIRE and WARFASA studies were independent, investigator-initiated, randomized, double-blind, placebo-controlled clinical trials designed to examine the efficacy and safety of low-dose aspirin in the extended treatment of VTE. Eligible patients were those with a first

episode of unprovoked VTE, defined as proximal deep-vein thrombosis (DVT) or pulmonary embolism (PE), who had completed initial treatment with heparin and warfarin or an equivalent anticoagulant regimen. Venous thromboembolism was considered as unprovoked when it occurred in the absence of any known specific permanent or temporary clinical risk factor. The main inclusion and exclusion criteria for the two studies are reported in **Supplementary Table 1**.

Patients in each trial received 100 mg enteric-coated aspirin or matching placebo (Bayer HealthCare, Germany) once daily and were followed up for recurrent VTE, arterial ischemic events (myocardial infarction and stroke), bleeding, and death. Both study protocols allowed for interruption of study medication (for example, for major surgery) and for anticoagulant thromboprophylaxis for situations of risk while on the study. Patients were followed up for at least 2 years in the WARFASA trial and up to 4 years in ASPIRE.

Design and rationale

Early in the recruitment phases of both studies, the management committees agreed to combine the data from the two trials in a prospective combined patient-level analysis. Both trials had been planned with harmonization of their study designs, including similar eligibility criteria, study interventions and definitions of outcomes.^{15,16} While it was recognized that the ASPIRE and WARFASA trials would provide important information, neither was powered for reliable estimates of moderate treatment effects on particular outcomes or within particular subgroups. With a planned 2000 patients, INSPIRE would have 80% power to detect a 30% reduction in VTE. Owing to slow recruitment, the final sample size of the combined trials was 1225, giving 80% power to detect a 35% reduction.

Outcome measures

The primary outcome for the INSPIRE study was recurrent VTE, defined as the occurrence of

newly diagnosed symptomatic VTE or fatal PE. Secondary outcomes were: 1. major vascular events: the composite of recurrent VTE, myocardial infarction, stroke, or cardiovascular death; and 2. recurrent VTE, myocardial infarction, stroke, all-cause mortality and major bleeding, a measure of the net clinical benefit. In addition the component outcomes were also reported separately in pooled analyses: PE, DVT, myocardial infarction, stroke and cardiovascular death. Safety outcomes included major bleeding and clinically relevant nonmajor bleeding. Definitions of these outcomes have been reported.^{15,16} All suspected study outcome events were adjudicated by the independent outcome assessment committees for the trials.

Statistical analysis

The primary efficacy analysis compared the treatment groups on the first occurrence of VTE from randomization to a maximum of 4 years using a modified intention-to-treat principle, which included all randomized patients who had received at least one dose of the study drug, and was stratified by trial. Tests for heterogeneity of treatment effect between trials on each outcome were done before the combined analyses. Hazard ratios (HRs), 95% confidence intervals and *P* values were estimated in an unadjusted Cox regression analysis, which was repeated for the secondary endpoints. Secondary analyses with adjustment for baseline risk factors were also prespecified. Survival curves were estimated by using the Kaplan-Meier procedure.

Subgroup analyses compared the effects of treatment across subgroups on the prespecified outcome of major vascular events (the composite of recurrent VTE, myocardial infarction, stroke, or cardiovascular death). The prespecified subgroups were the qualifying VTE event (DVT, PE, or both), sex, age groups (<50 years, 50<65, ≥65), anticoagulation duration (<6, 6<9, >9 months), body mass index (BMI) (<25, 25<30, ≥30 kg/m²). The primary subgroup analysis examined whether the relative treatment effects of aspirin differed across subgroup

categories, by using tests for treatment-subgroup interactions. The effect of treatment on reducing VTE was also examined in these subgroups within clinically relevant categories.

Nonadherence with study medication during extended follow-up was anticipated by planned additional analyses which were specified before the trial results were unblinded. The efficacy of aspirin in a hypothetical fully adherent group was estimated by adjusting the treatment effect in the intention-to-treat analysis by the nonadherence rates averaged over the study period; the nonadherence rate was defined as the proportion of patients assigned to aspirin who discontinued it plus the proportion of patients assigned to placebo who initiated antiplatelet or anticoagulation treatment.¹⁷ A more sensitive estimate of adherence-adjusted treatment effect considered the relative reduction in VTE due to aspirin treatment within each year of follow-up from randomization and within each trial. An adherence-adjusted estimate was then derived from a weighted combination of these estimates, using the average adherence rates within each year and study as weights (see Supplemental Methods for additional details). An on-treatment analysis restricted to information from patients while they were still on study treatment was also performed. All analyses used SAS, version 9.3 (SAS Institute).

Oversight of the study

The INSPIRE study was overseen by the International Steering Committee which had final referenceresponsibility for verification and analyses of the data (see Appendix). The protocols of each trial and the plan to undertake a prospective combined analysis were approved by the relevant independent ethics committees.^{15, 16} Written informed consent was obtained from all patients before randomization. The National Health and Medical Research Council (NHMRC (Australia)) Clinical Trials Centre (CTC) coordinated the analysis and checked the combined data set. Statistical analyses were undertaken at both the CTC and the Italian coordinating centre.

All authors contributed to the interpretation of the results and approved the final version of the paper. The INSPIRE combined analysis was supported by a grant-in-aid from the NHMRC.

Aspirin and placebo tablets for both trials were supplied by Bayer HealthCare. The NHMRC and Bayer HealthCare played no role in study design, data collection, or analysis of the individual trials or the INSPIRE project.

Results

Patients

Data from 1224 patients were included in the combined analyses: 402 from WARFASA and 822 from ASPIRE (**Figure 1**) (One patient did not receive any treatment and was excluded.) Baseline characteristics were well balanced between the two treatment groups pooled over the two studies (**Table 1**). Patients in the WARFASA study were older, more likely to be male and be smokers, but less likely to be obese (**Table 1**). Patients were followed up for a median 30.4 months. Within 4 years of randomization, 193 patients had at least one VTE event. Patients in the intention-to-treat analyses included 12 subsequently found to not meet eligibility criteria, 31 who withdrew consent for further follow-up, and 13 lost to follow-up. The median period that patients were on the study medication was 24.2 months.

Recurrent venous thromboembolism

During the follow-up period, VTE occurred in 112 of 608 patients (18.4%) assigned to placebo and 81 of 616 (13.1%) assigned to aspirin (a rate of 7.5% per year vs. 5.1% per year (**Figure 2** and **Table 2**). This was a 32% relative reduction in VTE (HR, 0.68; 95% CI, 0.51 to 0.90; $P=0.008$). This corresponds to needing to treat 42 patients each year to prevent one VTE event. After adjustment for baseline characteristics, the HR was similar (0.65; 95% CI, 0.49 to 0.86;

$P=0.003$) (**Figure 3**). There were four fatal recurrences of VTE (2 in each group). Aspirin reduced the rate of recurrent DVT without symptomatic PE by 34% (HR, 0.66; 95% CI, 0.47 to 0.92; $P=0.01$) and PE with or without symptomatic DVT by 34% (HR, 0.66, 95% CI, 0.41 to 1.06, $P=0.08$).

Secondary outcomes and bleeding events

Aspirin reduced the risk of major vascular events (symptomatic VTE, myocardial infarction, stroke, and cardiovascular death) by 34% (8.7% per year vs 5.7% per year), corresponding to 34 needed to treat per year to prevent an event. Clinically relevant bleeding occurred in 12 patients assigned placebo (7 of whom had a major bleed) and in 18 patients assigned aspirin (9 of whom had a major bleed). The rate of bleeding was low and did not differ significantly between the groups (0.7% per year for placebo and 1.1 % per year for aspirin). The net clinical benefit (symptomatic VTE, myocardial infarction, stroke, all-cause mortality and major bleeding) was improved with aspirin by 33% (9.8% per year vs 6.5% per year; number needed to treat (NNT), 31) (**Figure 2 and Table 2**).

Prespecified subgroups

Similar relative reductions in events were observed with aspirin in each of the prespecified subgroups, either in terms of the effect on VTE (**Figure 4**) or on major vascular events, the prespecified outcome for subgroups (**Figure 5**), with no significant interactions (each $p>0.1$). Larger absolute reductions in VTE occurred in those subgroups at higher risk of recurrent VTE: in men vs women (absolute risk reduction 3.3% per year vs 1.7% per year; NNT, 31 vs 59) and in older patients (≥ 65 vs <65 years, absolute risk reduction 5.5% per year vs 1.3% per year; NNT, 19 vs 78).

Treatment effects over time

The effects of aspirin in each year of follow-up after randomization are shown in **Figure 6**. The relative reduction in VTE events did not differ significantly over each year of follow-up (test for interaction by year, $P=0.31$). However, the absolute reduction in recurrent events was significantly greater in the first year when the risk of recurrence among untreated patients was higher. In the first year aspirin reduced VTE events by 5.6%, from 11.0% to 5.4% (HR, 0.49; 95% CI, 0.32 to 0.76; $P=0.001$).

Analyses adjusted for treatment adherence

During the follow-up period, 164 patients assigned to placebo and 154 patients assigned to aspirin discontinued the study drug, with rates of 13.4% per year and 11.4% per year, respectively (**Figure 7**). A total of 76 patients assigned to placebo and 68 assigned to aspirin initiated open-label antiplatelet therapy or anticoagulation therapy before a defined vascular event occurred. In 65 patients (32 placebo group, 33 aspirin group) an antiplatelet drug was used and in 79 patients (44 placebo group, 35 aspirin group) an anticoagulant drug was used with or without an antiplatelet drug. The combined rate of nonadherence with study medication in the placebo and aspirin groups, averaged over the study period, was 19.4%: 13.2% in the aspirin group discontinued aspirin and 6.2% in the placebo group initiated antiplatelet or anticoagulation treatment.

When the analysis was adjusted for nonadherence with medication (with the analysis weighted within each year and study), the relative reduction in the risk of VTE with aspirin was 42% (HR 0.58; 95% CI 0.40 to 0.85; $P=0.005$) (**Supplementary Table 2**). This would correspond to 32 patients treated each year to prevent one VTE event. The result was similar when the adherence-adjusted analysis was based simply on modifying the intention-to-treat estimate by the pooled nonadherence rate: a 40% reduction (HR, 0.60; 95% CI, 0.39 to 0.88;

$P=0.008$). An analysis based on the actual treatment received showed similar relative effects (HR, 0.63; 95% CI, 0.46 to 0.86, $P=0.004$).

Discussion

The prospectively planned combined analysis of the ASPIRE and WARFASA trials using individual patient data provides strong evidence that, in patients with a prior unprovoked VTE, aspirin after initial anticoagulation is ceased is effective in reducing the rate of recurrence of VTE. It builds on the previously reported trial results^{15, 16} and simpler meta-analysis,¹⁶ providing robust findings across important subgroups and outcomes. Aspirin reduces recurrent events by more than one-third, with similar reductions in symptomatic DVT and PE and similar effects on major vascular events (the composite secondary outcome). When thrombosis and bleeding events are considered together, there is clear evidence of a net clinical benefit favouring aspirin over placebo.

The design of this prospective combined analysis has the strengths of a larger individual randomized trial.¹⁸ Many aspects of ASPIRE and WARFASA were identical, including the randomized double-blind placebo-controlled design, the study interventions, and the outcome definitions. Study management committees jointly convened and further harmonized each study protocol with respect to eligibility criteria, efficacy and safety outcomes, and analysis plans. As this combined patient-level analysis was defined before any unblinding of study outcomes of either individual trial, it has the same scientific rigor as a single larger randomized study.

The INSPIRE study provides greater power than either trial to more reliably estimate treatment effects among predefined subgroups and to examine the treatment effects over time. These analyses demonstrate that the relative treatment effects are similar across these subgroups

and that the relative effect overall is still an appropriate estimate to consider for each subgroup. However, larger absolute effects of treatment are seen when there is a higher risk of recurrence, particularly for men compared with women and for older compared with younger patients. For treatment effects over time, there was not clear evidence of lesser effects over time. However, with more events occurring in the first year, there are larger *absolute* benefits of aspirin, and within first 12 months after anticoagulation is ceased when the risk of VTE recurrence is still at its highest. This information may be important for patients at high risk of recurrence for whom ongoing anticoagulation is not an option and for whom aspirin provides greater absolute benefit. Even among patients at lower risk, aspirin therapy still remains a useful treatment with a favorable risk-benefit profile.

A particular issue raised by intention-to-treat analyses of long-term trials is the problem of falling adherence to protocol therapy over time leading to an underestimation of the true effect of the study treatment. This can be especially problematic for a treatment such as aspirin, which is readily available as a nonprescription medicine. Estimating effects of fully adherent aspirin use, using an on-treatment analysis, is prone to selection bias. An alternative approach is to use a randomization-based efficacy estimate which inflates the size of the treatment effect by dividing the overall efficacy estimate by the average adherence rate.¹⁷ A refinement to this approach, with greater power, is to use a weighted combination of treatment effects within each year of follow-up with greater weight given to the earlier years when there is greater adherence to treatment. These approaches gave similar qualitative conclusions and suggest that in a fully adherent population aspirin will prevent about 40% of recurrent events.

It is clear that the treatment effect of aspirin is still much less than can be achieved with warfarin or the new oral agents with direct thrombin inhibitors⁹⁻¹² or factor Xa inhibitors,^{13,14}

where more than an 80% reduction in events might be expected. Consequently, aspirin represents a reasonable treatment option only in patients who would otherwise not be receiving oral anticoagulation.

While the current combined analyses have strengths, there are also limitations to the study and its conclusions. Because patients with cancer represented only a small proportion of patients in ASPIRE and were excluded from WARFASA and because patients with known coronary heart disease were not included in either study, our results do not apply to all patients with VTE. Further, the combined analyses provide clearcut evidence of treatment benefit but have limited power to assess the longer-term effects of aspirin on VTE.

Globally, many patients with unprovoked VTE are not routinely treated with longer-term anticoagulant therapy. We conservatively estimate that over a million patients worldwide experience unprovoked VTE each year and an even greater number have a prior history of unprovoked VTE.^{19,20} Less than half of these patients remain on long-term anticoagulant therapy.^{21–23} If a million patients worldwide could be treated with aspirin each year, a hundred thousand events might be prevented with a minimal increase in bleeding (about 1 extra major bleed for every 25 VTEs prevented) and with a treatment that would also be cost saving (the costs of treating subsequent VTEs avoided would outweigh the cost of aspirin). Additional potential benefits of aspirin in treated patients would include a reduction in arterial vascular events and cancer-related events, each known to be associated with VTE.^{24–27}

In conclusion, this prospective combined analysis of the WARFASA and ASPIRE trials provides clear evidence that aspirin reduces the risk of recurrent VTE events by about 40% and is a very safe and effective therapy. Although it does not reduce the rate of VTE by as much as vitamin K antagonists or newer oral anticoagulants (direct thrombin inhibitors or factor Xa

inhibitors), among patients for whom such therapies are not considered appropriate or are discontinued, aspirin should be strongly considered.

Funding Sources: The ASPIRE study was funded by grants from the National Health and Medical Research Council (Project grants 301911 (2003) and 570967 (2008)), New Zealand Health Research Council (HRC) (05/080R (2005)), New South Wales Health, and Australian Society of Thrombosis and Haemostasis. The WARFASA study was funded by the University of Perugia and a grant-in-aid from Bayer HealthCare. The study drug (aspirin and placebo) for both studies was provided by Bayer HealthCare.

Appendix

INSPIRE International Steering Committee

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ASPIRE Outcomes Assessment Committee

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Conflict of Interest Disclosures: None.

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Table 1. Baseline characteristics by study and by randomized treatment.

Characteristic	Study		<i>P</i> *	Treatment	
	ASPIRE	WARFASA		Placebo	Aspirin
Number	822	402		608	616
Age (years) (mean±SD)	54±16	61±15	<0.001	57±16	57±16
Male sex (<i>n</i> (%))	447 (54)	257 (64)	0.002	343 (56)	361 (59)
Body mass index (kg/m ²) (mean±SD)	29±6	27±4	<0.001	28±5	29 ± 6
Normal (<25) (<i>n</i> (%))	207 (25)	116 (29)	<0.001	161 (26)	162 (26)
Overweight (25<30) (<i>n</i> (%))	313 (38)	199 (50)		264 (43)	248 (40)
Obese (≥30) (<i>n</i> (%))	300 (36)	82 (20)		181 (30)	201 (33)
Qualifying event (<i>n</i> (%))					
DVT only	468 (57)	252 (63)	0.36	362 (60)	358 (58)
PE only	231 (28)	55 (14)		137 (23)	149 (24)
DVT and PE	115 (14)	95 (24)		105 (17)	105 (17)
Duration of anticoagulation					
<6 months	224 (27)	28 (7)		110 (18)	142 (23)
6<9 months	387 (47)	176 (44)		291 (48)	272 (44)
9<12 months	137 (17)	87 (22)		103 (17)	121 (20)
≥12 months	74 (9)	111 (28)		104 (17)	81 (13)
Anticoagulation to randomization (days) (median (Q1 to Q3))	7 (1–29)	1 (0–7)	<0.001	5 (1–22)	4 (1–21)
Current smoker (%)	73 (9)	65 (16)	<0.001	69 (11)	69 (11)
Active malignancy at baseline (%)	18 (2)	0		7 (2)	11 (3)
Low-molecular-weight heparin	711 (86)	326 (81)	0.04	522 (86)	515 (84)
Unfractionated heparin	52 (6)	60 (15)		52 (9)	60 (10)
Other	59 (7)	16 (4)		34 (6)	41 (7)
Subsequent therapy (<i>n</i> (%))					
Low-molecular-weight heparin	9 (1)	0	<0.001	4 (0.7)	5 (0.8)
Warfarin	684 (83)	402 (100)		538 (88)	548 (89)
Other	129 (16)	0		66 (11)	63 (10)

* *P* values for the comparison of the baseline variables between the studies are for a chi-squared analysis for binary variables, ordinal regression analysis for multiple categories (ordered) variables, *t* test for normally distributed continuous variables, and a Kruskal–Wallis test for non-normal data.

Table 2. Outcome events, according to randomized treatment*.

Endpoint	Placebo (n=608)		Aspirin (n=616)		Hazard ratio with aspirin (95% CI)	P
	Events (n)	% per year	Events (n)	% per year		
Recurrent venous thromboembolism	112	7.5	81	5.1	0.68* (0.51–0.90)	0.008
Deep-vein thrombosis only	85	5.5	59	3.6	0.66 (0.47–0.92)	0.01
Pulmonary embolism with or without deep-vein thrombosis	42	2.6	29	1.7	0.66 (0.41–1.06)	0.08
Major vascular event†	129	8.7	91	5.7	0.66 (0.50–0.86)	0.002
Myocardial infarction	7	0.4	4	0.2		
Stroke	5	0.4	7	0.4		
Cardiovascular death	9	0.5	6	0.3		
Bleeding	12	0.7	18	1.1	1.50 (0.72–3.14)	0.28
Major	7	0.4	9	0.5	1.24 (0.46–3.33)	0.67
Clinically relevant nonmajor bleeding	5		9			
Major vascular event, major bleeding or death from any cause	144	9.8	103	6.5	0.67 (0.52–0.86)	0.002
Death from any cause	23	1.4	20	1.2	0.84 (0.46–1.53)	0.56
Pulmonary embolism	2		2			
Myocardial infarction	2		1			
Other cardiovascular cause including sudden death of uncertain cause	5		3			
Cancer	6		7			
Bleeding	2		0			
Other noncardiovascular cause	6		7			

* Only the first event for each patient is counted in each row. Hazard ratio and 95% confidence intervals estimated by Cox regression analysis stratified by trial. Tests for treatment-trial interaction for each outcome were not significant (each $P > 0.20$).

† Composite of venous thromboembolism, myocardial infarction, stroke and cardiovascular death.

Figure Legends:

Figure 1. Consort flow diagram.

Figure 2. Cumulative risk of outcome events. Panel A: venous thromboembolism (VTE), defined as symptomatic deep-vein thrombosis or pulmonary embolism; Panel B: major vascular events (composite of recurrent VTE, myocardial infarction, stroke, and cardiovascular death); Panel C: The reduction in the risk of recurrent VTE, myocardial infarction, stroke, all-cause mortality, and major bleeding is a measure of the net clinical benefit of aspirin treatment.

Figure 3. Effects of aspirin treatment on recurrent venous thromboembolism and other outcomes after adjustment for baseline characteristics: age (<50 years, 50<65, ≥65), sex (male versus female), qualifying event (deep-vein thrombosis only versus pulmonary embolism with or without deep-vein thrombosis), body mass index (normal, overweight, obese) and duration of anticoagulation (<6, 6 to <9, ≥9 months).

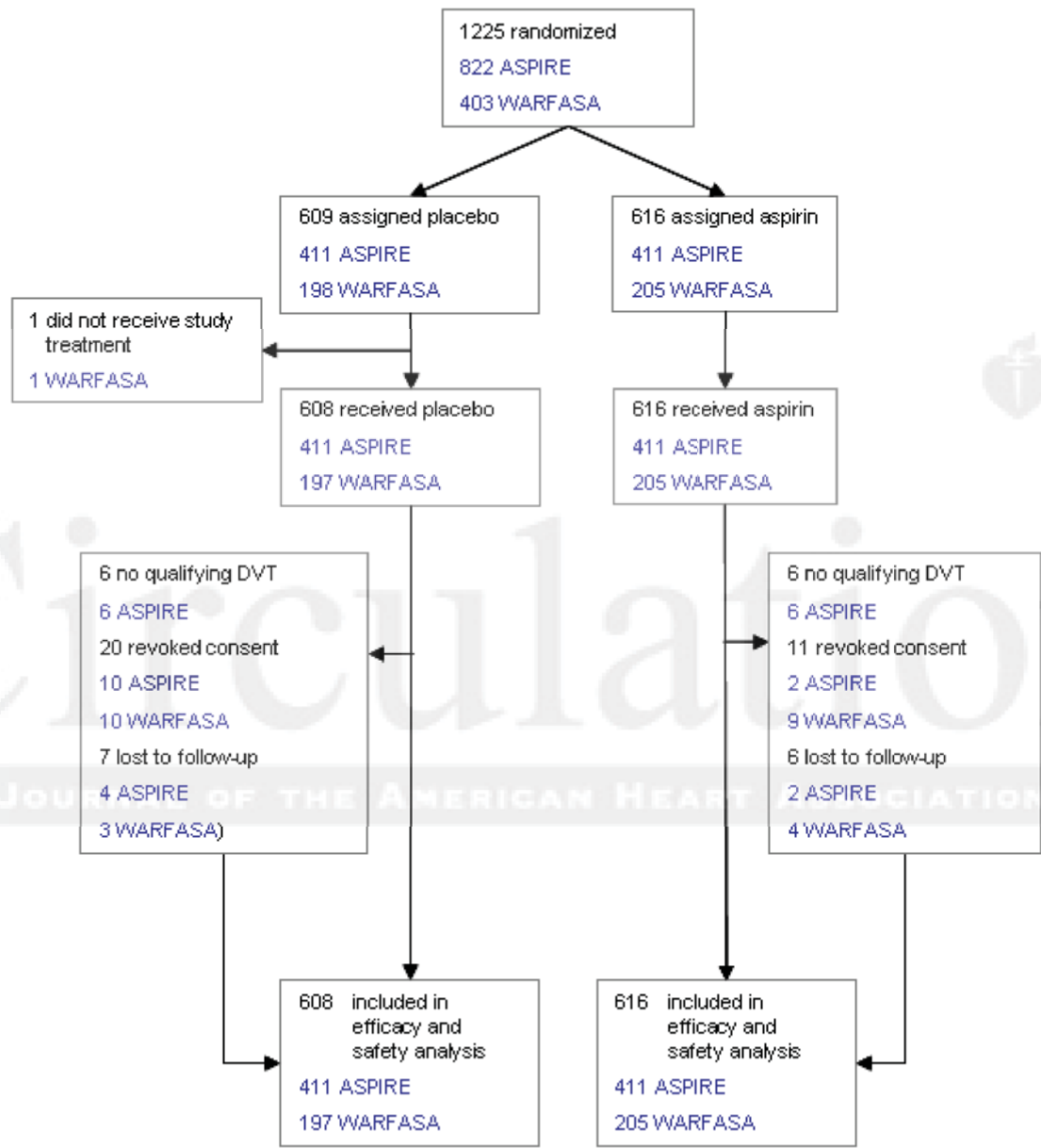
Figure 4. Effects of aspirin treatment on venous thromboembolism in prespecified subgroups.

**P* for trend.

Figure 5. Effects of aspirin treatment on major vascular events in prespecified subgroups. **P* for trend.

Figure 6. Effects of treatment on venous thromboembolism in each year of follow-up.

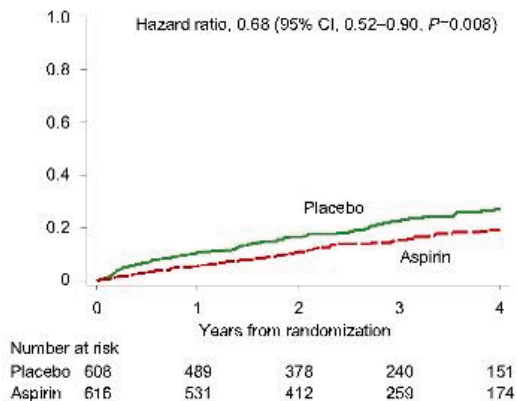
Figure 7. Kaplan-Meier curves of adherence with study medication (shown as time to permanent discontinuation) and cumulative risk curves of uptake of open-label antiplatelet therapy or anticoagulation therapy, by treatment group.



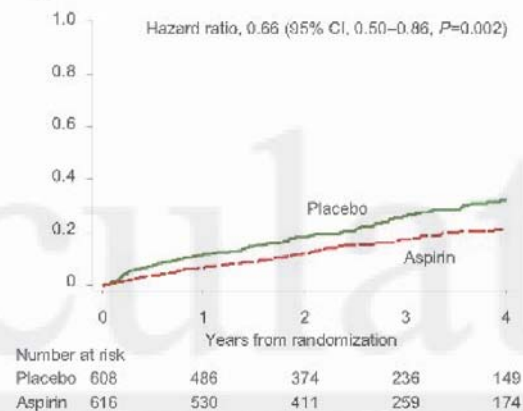
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Figure 1

Venous thromboembolism



Major vascular event



Net clinical benefit

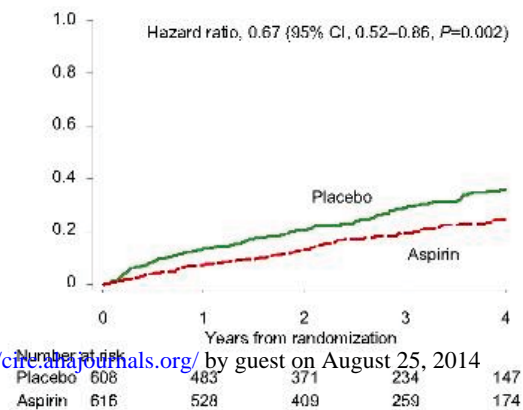


Figure 2

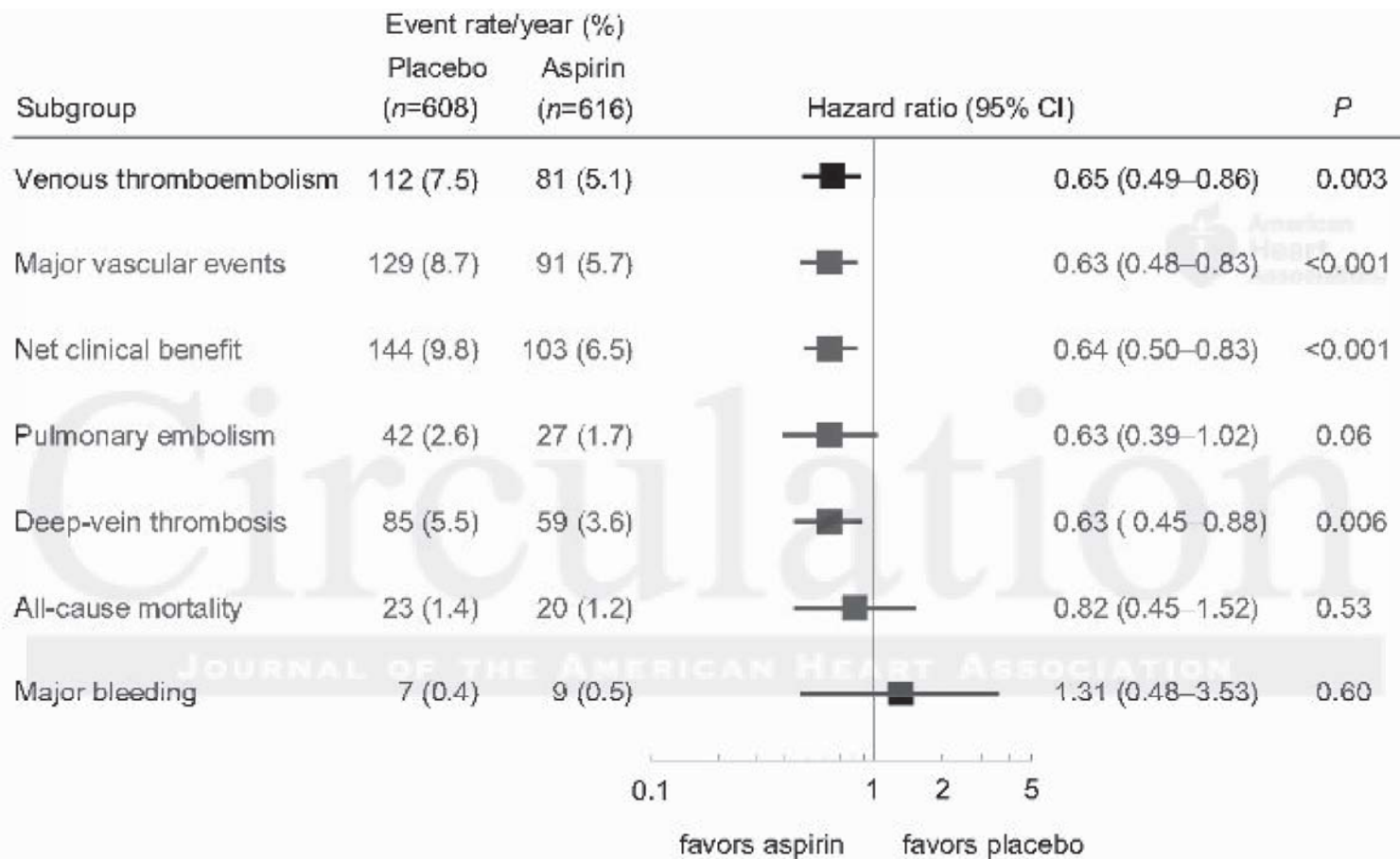


Figure 3

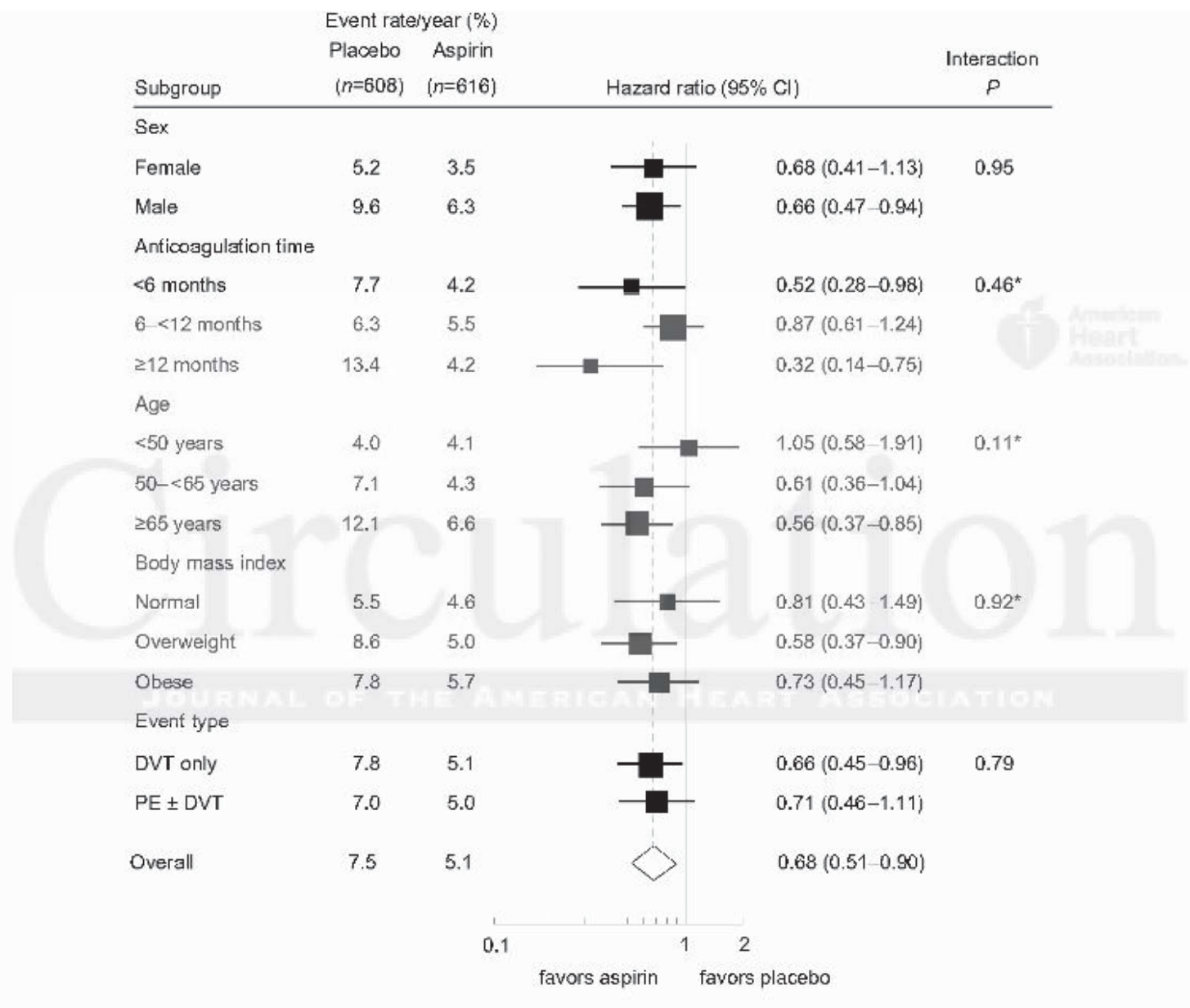


Figure 4

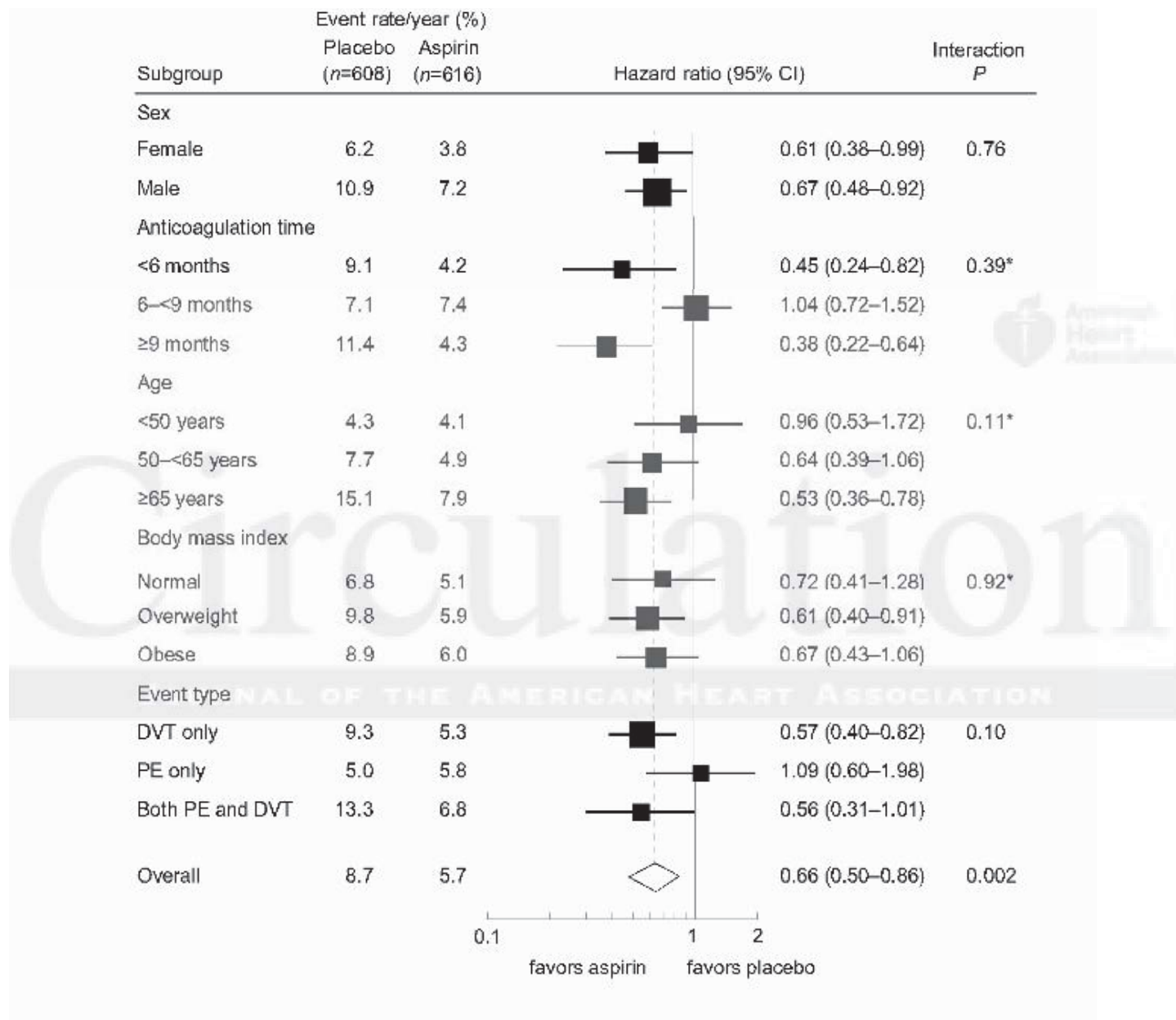


Figure 5

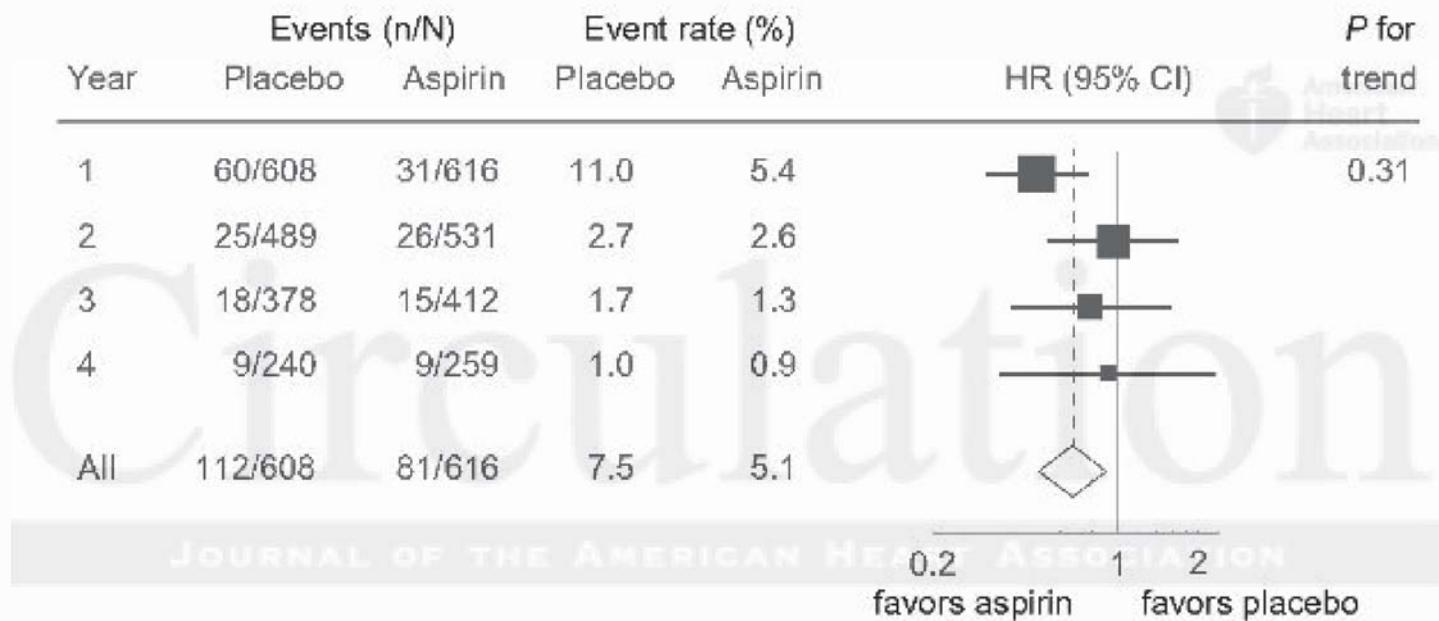
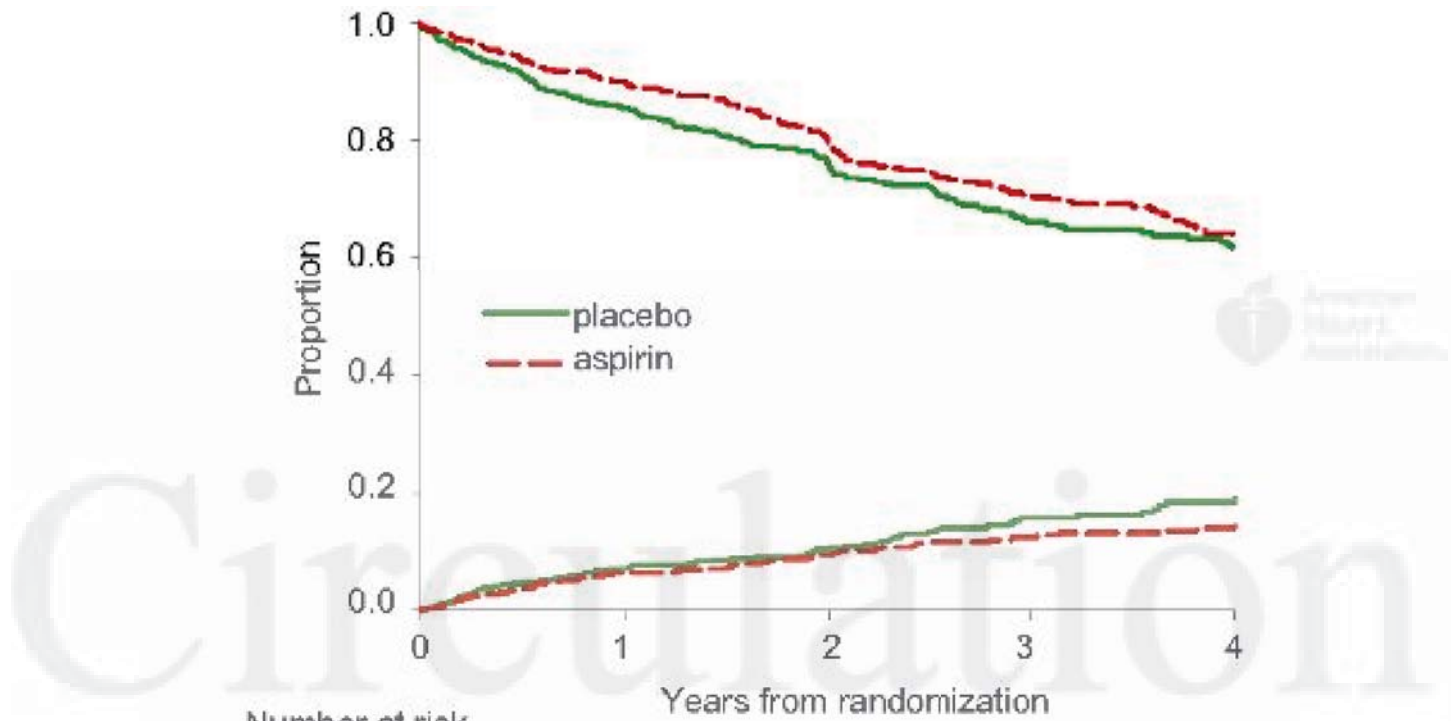


Figure 6



Number at risk

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Drop-in

Placebo	608	454	335	192	116
Aspirin	616	504	382	230	150

Drop-out

Placebo	608	432	294	154	89
Aspirin	616	485	339	181	98

Figure 7

Supplemental Material

Supplemental Methods

Adherence adjustment method

For each trial, the log hazard ratio ($\ln(HR)$) and its variance (v) were calculated for each year of follow-up. These estimates were adjusted for adherence by dividing the $\ln(HR)$ for each year by the average adherence ($c = 1 - p_{disc} - p_{drop-in}$) for the middle of that year

$$adj(\ln HR) = \frac{\ln(HR)}{(1 - p_{disc} - p_{drop-in})}$$

where p_{disc} is the proportion of patients, randomized to active treatment, who discontinue study medication and $p_{drop-in}$ is the proportion randomized to placebo who commence aspirin or an equivalent medication.

The variances for the estimates were adjusted in the same way

$$Var(adj(\ln HR)) = \frac{var(\ln(HR))}{(1 - p_{disc} - p_{drop-in})^2}$$

Weights were calculated as

$$w = 1/Var(adj(\ln HR)).$$

A weighted meta-analysis was conducted by multiplying the adjusted value for each year by w and the variances by w^2 . The values were combined by summing the weighted estimates and dividing by the sum of the weights

$$weighted\ adj_lnHR = \frac{\sum w * adj_lnHR}{\sum w},$$

to produce a grand total (G). Similarly, the variances weighted by w^2 were combined to give a pooled variance V

$$V = Var(weighted\ adj_lnHR) = \frac{\sum w^2 * var}{(\sum w)^2}$$

The value $\exp(G/V)$ was then the overall event rate ratio.

Supplemental Table 1: Summary of eligibility criteria

	ASPIRE	WARFASA
Inclusion	Age >18	No age restriction
	First unprovoked deep-vein thrombosis or pulmonary embolism (no transient risk factor)	First idiopathic deep-vein thrombosis or pulmonary embolism (no known risk factor)
	Initial unfractionated heparin / or low-molecular-weight heparin and warfarin	Initial unfractionated heparin or low-molecular-weight heparin and warfarin
	Recommended 6 to 24 months treatment	Recommended 6 to 12 months treatment
Exclusion	Indication or contraindication for aspirin	Indication or contraindication for aspirin
	Indication for antiplatelet or oral anticoagulation	Indication for antiplatelet or oral anticoagulation
	(Thrombophilia not excluded except at discretion of investigator)	Known thrombophilia excluded (including lupus anticoagulants, anticardiolipin antibodies, homozygous or combined Factor V Leiden mutation and prothrombin gene mutation, antithrombin deficiency, cancer)
	(Cancer not excluded, except at discretion of investigator)	History of cancer
	Increased bleeding risk	Increased bleeding risk
	COX 1 or COX 2 inhibitor	COX 1 or COX 2 inhibitor
	Life expectancy <12 months	Life expectancy <6 months
	Expected nonadherence	Expected nonadherence
	Anticipated difficult follow-up	Anticipated difficult follow-up

Supplemental Table 2: Unadjusted and adherence-adjusted* effect of aspirin in each year, and overall

Year	Unadjusted effect of aspirin		Adherence-adjusted effect of aspirin	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
1	0.49 (0.32–0.76)	0.001	0.45 (0.28–0.74)	0.002
2	0.97 (0.55–1.71)	0.92	0.92 (0.44–1.89)	0.81
3	0.79 (0.40–1.59)	0.51	0.65 (0.21–2.04)	0.46
4	0.88 (0.34–2.29)	0.79	0.88 (0.13–5.73)	0.89
All years	0.68 (0.51–0.91)	0.008	0.58 (0.40–0.85)	0.005

* The efficacy of aspirin in a fully adherent group was estimated by adjusting the treatment effect in the intention-to-treat analysis by the nonadherence rates (the proportion of patients assigned to aspirin who discontinued it plus the proportion of patients assigned to placebo who initiated antiplatelet or anticoagulation treatment) averaged within each year and study. An adherence-adjusted estimate for all years was derived from a weighted combination of the estimates from each year and study (see Supplemental Methods).