# WARFASA: Aspirin for Preventing the Recurrence of Venous Thromboembolism[1]

**WARF**arin and **A**cetyl**S**alicylic **A**cid Study

## BOTTOM LINE

- In patients whom have had a first unprovoked VTE with low to moderate bleed risk, the addition of ASA 100 mg daily is reasonable to prevent future DVT not PE or mortality events, if the decision is made to stop VKA; however, in patients at high risk for recurrence extended anticoagulant therapy should be considered first line. {ASA is not a replacement for warfarin or newer anticoagulants in the initial treatment of VTE.}

## BACKGROUND

- Chest 2012 guidelines suggest that in patients with unprovoked DVT/PE there should be at least 3 months of anticoagulation. After 3 months of treatment, patients should be evaluated for the risk versus benefit ratio of extended therapy Risk for recurrence: Male, Obesity, Positive D-Dimer at end of anticoag., residual vein obstruction, hereditary and acquired thrombophillia, post thrombotic syndrome.[2]
- In patients with a first VTE/PE that is unprovoked and who have a low or moderate bleeding risk, the Chest 2012 guidelines suggest extended anticoagulant therapy over 3 months. There is no mention of ASA for long term therapy in the guidelines.[2]
- Results from the Antiplatelet Trailists' Collaboration (ATC) meta-analysis showed that ASA reduced the incidence of deep-vein thrombosis (DVT) by 20 % and that of Pulmonary Embolism(PE) by 69% compared to placebo in patients at high risk for thromboembolic events Primary prevention of VTE. Patients with acute or previous vascular disease or some other predisposing condition.[3]
- Results of an analysis of the Women's Health Study looking at occurrence of $VTE_{2^o\ endpoint}$ were in contrast to the ATC trial showing no significant difference in VTE or PE with ASA 100 mg every other day compared to placebo in healthy women Primary Prevention >45,no history of CHD,CVD, cancer or other major diseases.[4]
- Prior to the WARFASA trial there was no evidence looking at secondary prevention of VTE in patients who have discontinued warfarin. The aim of the WARFASA study was to assess the clinical benefit of aspirin for the prevention of recurrence after a course of treatment with VKA in patients with unprovoked venous thromboembolism.

## TRIAL BACKGROUND[1,5,6,7,8]

**DESIGN**: Randomized Allocation Concealed, multi-centre 25 sites in European centers from May 2004 - Aug 2010, intention-to-treat, double-blind adjudication committee,unclear who else was blinded , placebo-controlled, investigator-initiated. Supported by grant-in-aid from Bayer healthcare, data analysed by clinical research unit of the University of Perugia. Two substantial protocol amendments: Changed to an event driven design; change of primary endpoint to VTE only.

**INTERVENTION**: Aspirin 100 mg daily versus placebo

**INCLUSION**: >18 years old treated with vitamin K antagonist for 6 to 18 months 90% 6-12 months for first-ever, objectively confirmed, symptomatic, unprovoked absence of any known risk factor proximal DVT, PE or both where a decision was made to discontinue VKA therapy randomization 2 weeks after vitamin K antagonist stopped.

**EXCLUSION**: Known cancer, major thrombophilia, an indication for long-term anticoagulant therapy other than VTE, previous symptomatic complications of atherosclerosis requiring treatment with aspirin or other anti-platelet agents, **active bleeding risk or high risk for bleeding or a bleeding episode which occurred during the 6-18 months of anticoagulation**, allergy or intolerance to aspirin, life expectancy <6 months, anticipated non-adherence to study medication, pregnancy or breastfeeding, women with thromboembolism associated with the use of estro-progestin therapy.

**POPULATION** at baseline (n=403 over 2 years): Age 62 ± 15 years; ~65% ♂; BMI 27 kg/m$^2$ ± 4, 99% Caucasian; index event DVT ~60 % ASA, ~66 % placebo; index event PE ~ 41% ASA, ~34 % placebo; Duration of VKA before randomization - 6 months ~37 % ASA,~ 32 % placebo; 12 months ~55 % ; 18 months ~9 % ASA, ~12 % placebo No significant differences in baseline characteristics between the two study groups.

## TABLE 1:RESULTS

Follow-up: mean ~ 25 months

| Clinical Endpoints | Aspirin (n=205) | | Placebo (n=197) * | | HR (95% CI) | p-value | ARR/NNT (mean 25 months follow-up) | Comments |
|---|---|---|---|---|---|---|---|---|
| | ITT | On treatment | ITT | On treatment | | | | |
| **PRIMARY ENDPOINT:** | | | | | | | | |
| **Primary Endpoint:** Composite of fatal and non-fatal pulmonary embolism, and deep-vein thrombosis | 6.6%/yr (n=28) | 5.9%/yr (n=23) | 11.2%/yr (n=43) | 11.0%/yr (n=39) | 0.58 (0.36-0.93) | 0.02 | 4.6%/ 21/yr | First Coprimary Endpoint: Assumed a 40 % relative risk reduction with aspirin with 70 events to provide a power of 80 % |
| **Individual Primary Endpoint**: Pulmonary embolism | 5.3% (n=11) | NR | 7.1% (n=14) | NR | NS | 0.37 | - | Subgroup analysis<br>- 6.7%/yr ASA group who entered the study because of pulmonary embolism had a recurrent event as compared with 13.5%/yr in placebo group (p=0.02)<br>- Independent risk factors for recurrent VTE were >65 yr (HR 2.26); and male sex (HR 2.02) |
| **Individual Primary Endpoint:** Deep-vein thrombosis | 7.8% (n=16) | NR | 14.2% (n=28) | NR | 0.51 (0.27-0.94) | 0.03 | 6%/ 16/ ~2 yr | |
| SECONDARY ENDPOINTS | | | | | | | | |
| Death from any cause | 2.9% (n=6) | NR | 2.5% (n=5) | NR | NS | 0.95 | - | Secondary Endpoints: Arterial events included 4 MI's, 2 USA, 4 Ischemic strokes, 1 TIA, 4 acute lower limb ischemia. |
| Arterial event | 3.9% (n=8) | NR | 2.5% (n=5) | NR | NS | 0.53 | - | |

## TABLE 2: ADVERSE EVENTS

| Event | Aspirin (n=205) | Placebo (n=197) | p-value | NNH | Comments |
|---|---|---|---|---|---|
| Non-fatal major bleeding | 0.48 % (n=1) | 0.51% (n=1) | NS | - | Non-fatal major bleeding included 1 patient with gastric ulcer in the placebo group and 1 bowel angiodysplasia in the ASA group |
| Clinically relevant non-major bleeding | 1.4 % (n=3) | 1.5% (n=3) | NS | - | Reasons for discontinuation included gastric pain (2 placebo,1 ASA), a cutaneous reaction and renal failure in ASA treated patients. |
| Any adverse event leading to treatment discontinuation | 1.4% (n=3) | 1.0% (n=2) | NS | - | |

*** Modified ITT analysis= 198 randomized, 197 received 1 dose of study drug**

TABLE 2 :WARFASA + ASPIRE POOLED[9]

| EVENT | ASPIRIN (n=616) | PLACEBO (n=608) | HR (95% CI) | P-VALUE | ARR/NNT | COMMENTS |
|---|---|---|---|---|---|---|
| Rate of recurrence of VTE | 14% (n=85) | 19% (n=116) | 0.68 (0.51-0.90) | 0.007 | 5%/20 | Major vascular events is a composite of VTE ,MI, stroke, or CV death |
| Major Vascular events | 16 % (n=98) | 22 % (n=136) | 0.66 (0.51-0.86) | 0.002 | 6%/17 | |
| Clinically relevant bleeding | 2.9% (n=18) | 1.9% (n=12) | 1.47 (0.70-3.08) | 0.31 | - | |

See the RxFiles ASPIRE Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/Aspirin-warfarin-trial-summary-ASPIRE.pdf

## STRENGTHS, LIMITATIONS, & UNCERTAINTIES[1,2,7,8]

**STRENGTHS:**

- The first prospective, randomized, controlled trial that looked at hard outcomes with the use of ASA for secondary prevention of VTE in patients in whom vitamin K antagonist therapy had been discontinued.

**LIMITATIONS:**

- Exclusion of patient's with active bleeding risk or high risk for bleeding or a bleeding episode which occurred during the 6-18 months of anticoagulation high bleed risk: GI bleed within last 12 mo, endoscopic diagnosis of PUD or ulcerative esophagitis within the past 6 mo,intracranial bleeding within the last year, known bleeding diathesis. Exclusion of this patient population from the trial limits the generalizability May have had lower than expected bleeds due to ASA than would see in the general population
- Underpowered for 2° outcome of arterial event
- Method for diagnosis of recurrent DVT venous compression ultrasonography has a false positive rate of 14% which may have accounted for observed difference
- Slow recruitment of patients took 6 years to complete
- Small very specific sample size

**UNCERTAINITIES:**

- Applicability to non-caucasian individuals
- 2012 Chest guidelines suggest VKA therapy for 3 months but minimum in this study was 6 months[2]

♂=male,**2°**=Secondary, **ARR**=Absolute risk reduction, **ASA**=Acetylsalicylic Acid, **CHD**=Coronary heart disease, **CVD**=Cerebrovascular disease, **DVT**=Deep vein thrombosis, **HR**= Harm Ratio, **ITT**=Intention to treat, **MI**=Myocardial Infarction, **NR**=Not reported, **NS**=Non-significant, **NNT**=Number needed to treat,**NNH**=Number needed to harm, **PE**=Pulmonary embolism, **TIA**= Transient ischemic attack, **USA**= Unstable angina, **Vitamin K antagonist**=Warfarin, **VKA**=Vitamin K antagonist, **VTE**=Venous Thromboembolism, **Yr**=Year



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