ASPIRE: Low-Dose Aspirin for Preventing Recurrent Venous Thromboembolism[1]

Aspirin to Prevent **Re**current Venous Thromboembolism

BOTTOM LINE

- In patients whom have had an unprovoked VTE with low to moderate bleed risk the addition of ASA 100 mg daily is reasonable to prevent future VTE events and major vascular events if the decision is made to stop oral anticoagulation. {ASA is not a replacement for warfarin or newer anticoagulants in the initial treatment of VTE.}

BACKGROUND[1,2,3]

- Chest 2012 guidelines suggest that in patients with unprovoked DVT/PE there should be at least 3 months of anticoagulation. After 3 months a risk versus benefit evaluation should be conducted and if the patient is low/moderate risk for bleed extended therapy should be considered. [2]
- Results from the WARFASA trial suggested that in pts treated initially with a VKA for unprovoked VTE, starting ASA 100 mg daily once the VKA was stopped resulted in a significant reduction in future VTE events [2] See RxFiles Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/Aspirin-warfarin-trial-summary-WarfASA.pdf
- The objective of the ASPIRE study was to add to current literature and evaluate the efficacy of low-dose aspirin as compared to placebo, in preventing a recurrence of VTE in patients who had completed initial anticoagulation after a first unprovoked episode of VTE.

TRIAL BACKGROUND[1,4,5]

DESIGN: Randomized Stratified to duration of oral anticoag.>26 weeks or ≤ 26 weeks, intention-to-treat, double-blind allocation concealed, patient blinded, adjudication committee blinded placebo-controlled. Supported by National health and research council (Australia),Health research council (New Zealand), Austral-asian Society of Thrombosis and Hemostasis,Australia national heart foundation, and BAYER Healthcare. A priori plans to pool results of the ASPIRE and WARFASA trials in a prospectively planned meta-analysis.

INTERVENTION: Aspirin 100 mg daily versus placebo for a minimum of 2 years

INCLUSION: >18 years old with first unprovoked episode of objectively diagnosed symptomatic DVT popliteal or proximal leg vein , or and acute pulmonary embolism treated with warfarin or an alternative anticoagulant for 6 weeks to 24 months recommended INR 2-3 for 6-12 months.VTE was considered unprovoked in the absence the following risk factors in the preceding 2 months:confined to bed for > 1 week, major surgery, trauma requiring a cast, pregnancy or puerperium, and the use of oral contraceptives or HRT.

EXCLUSION: VTE > 2 years ago, another indication or contraindication to ASA,other anti-platelet therapy or NSAID, continuing indication for oral anticoagulant, other medical problems that would interfere with participation in the trial or limit life expectancy,active bleeding or at high risk of bleeding not included in trial exclusion criteria, in supplemental material.

POPULATION at baseline (n=822 over 2 years): Age ~54 ± 16 years; ~55% ♂; index event DVT ~60 %; index event PE ~ 30 %; ~65 % anti-coagulated for 6 to <12 months;Warfarin as anticoagulant ~80 %; Other direct thrombin inhibitors, factor Xa inhibitors ~15 %.No significant differences in baseline characteristics between the two study groups

TABLE 1: RESULTS[1,5]

Follow-up: mean ~ 37 months

Clinical Endpoints	Aspirin (n=411)		Placebo (n=411)		HR (95% CI)		p-value		ARR/NNT	Comments
	ITT	On Treatment	ITT	On Treatment	ITT	On Treatment	ITT	On Treatment		
PRIMARY ENDPOINT:										
Primary Endpoint: Composite of objectively confirmed DVT, fata/non-fatal PE	4.8%/yr (n=57)	4.8 %/yr	6.5%/yr (n=73)	7.6 %/yr	0.74 (0.52-1.05)	0.65 (0.44-0.96)	0.09	0.03	-	**Primary Endpoint:** Initially designed to have 90 % power to detect a relative risk reduction of 30 % enrolling 3000 patients. After protocol amendments enrolment was dropped to 1500 which would have 80% power to detect a 30 % risk reduction. During follow-up 32% of patients in the placebo group and 28% of patients in the active treatment group discontinued therapy(p=0.06)→ could be a contributing factor why ITT is non-significant.
INDIVIDUAL PRIMARY ENDPOINT	ITT		ITT		ITT		ITT		ITT	
Individual Primary Endpoint: PE with or without DVT	1.5% (n=18)		2.7% (n=20)		0.57 (0.32-1.02)		0.06		-	
Individual Primary Endpoint: Deep-vein thrombosis	3.3%/yr (n=39)		3.8%/yr (n=43)		0.86 (0.56-1.33)		0.50		-	
SECONDARY ENDPOINTS	ITT		ITT		ITT		ITT		ITT	
Net clinical benefit composite ↓ of VTE, MI, stroke, major bleeding or death from any cause	6 %/yr (n=71)		9 %/yr (n=99)		0.67 (0.49-0.91)		0.01		3 % 33/yr	Absolute numbers of MI,stroke and CV death not reported
Major vascular event composite of VTE, MI, stroke, or cardiovascular death	5.2 %/yr (n=62)		8 %/yr (n=88)		0.66 (0.48-0.92)		0.01		2.8% 35/yr	

TABLE 3: ADVERSE EVENTS

Event	Aspirin (n=411)	Placebo (n=411)	p-value	NNH	Comments
Major or clinically relevant non-major bleeding	1.1 %/yr (n=14)	0.6 %/yr (n=8)	0.22	-	More patients in the ASA group discontinued therapy due to GI adverse effects or bleeding (14 vs 2) than placebo. Bleeding episodes that did not meet the definition of major bleeding were only considered clinically relevant if they lead to discontinue of the study drug for >14 days
Clinically relevant non-major bleeding	1.5 % (n=6)	0.5% (n=2)	NR	-	
Major bleeding	2 % (n=8)	1.5% (n=6)	NR	-	

TABLE 2 :WARFASA + ASPIRE POOLED

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	-	

STRENGTHS, LIMITATIONS, & UNCERTAINTIES[1,2,3,4,5]

STRENGTHS:

- Added to the evidence from the WARFASA trial suggesting that ASA low dose can be used to prevent VTE in patients whom have stopped oral anticoagulants.

LIMITATIONS:

- Exclusion of patient's with active bleeding risk or high risk for bleeding 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. A potential reason that a person may not qualify for long term treatment of vitamin K antagonist is high bleed risk. 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
- Inadequate recruitment→ underpowered to detect a difference in primary outcome and bleeding.
- High drop out rate (~30 %)
- 2° outcome of major vascular event and net clinical benefit composites with primary outcomes→may have driven the benefit seen
- Method for diagnosis of recurrent DVT venous compression ultrasonography has a false positive rate of 14% which may have accounted for observed difference.

UNCERTAINITIES:

- Generalizability →a very specific patient population may benefit from ASA
- Would high bleed risk patients benefit?

♂=male,**2°=**Secondary, **ARR=**Absolute risk reduction, **ASA**=Acetylsalicylic Acid, **CHD=**Coronary heart disease, **CVD=**Cerebrovascular disease, **CV=** Cardiovascular,**CI=**Confidence interval, **DVT=**Deep vein thrombosis, **HR=** Harm Ratio,**GI=**Gastrointestinal, **HRT=**Hormone replacement therapy, **ITT=**Intention to treat,**INR=**International normalized ratio, **MI=**Myocardial Infarction, **NR=**Not reported, **NS=**Non-significant, **NNT=**Number needed to treat,**NNH=**Number needed to harm, **NSAID=** Non-steroidal anti-inflammatory drug, **PE=**Pulmonary embolism, **PUD=** Peptic Ulcer Disease ,**TIA=** Transient ischemic attack, **USA=** Unstable angina, **Vitamin K antagonist=**Warfarin, **VKA=**Vitamin K antagonist, **VTE=**Venous Thromboembolism, **Yr=**Year

REFERENCES:

[1] Brighton T, Eikelboom J, Mann K, Mister R, Gallus A, et al. Low-Dose Aspirin for Preventing Recurrent Venous Thromboembolism. N Engl J Med 2012;367:1978-1987

[2] Guyatt G, Akl A, Crowther M, Gutterman D,Schuunemann H, etal.Executive summary: Antithrombotic Therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:7S-41S

[3] Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, etal. Aspirin for Preventing the Recurrence of Venous Thromboembolism (WARFASA). N Engl J Med 2012;366:1959-67

[4] Supplemental Appendix to: Brighton T, Eikelboom J, Mann K, etal. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med 2012;367:1979-1987

[5] Protocol for: Brighton T, Eikelboom J, Mann K, etal. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med 2012;367:1979-1987