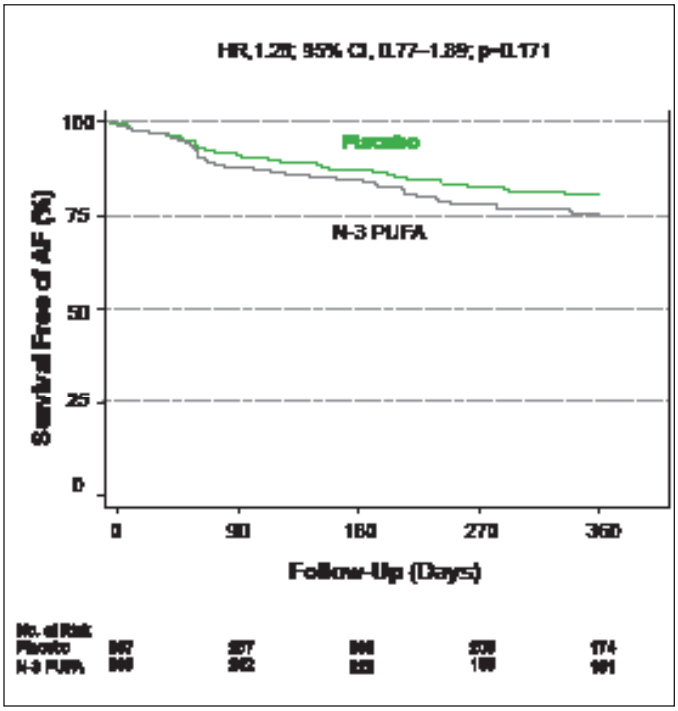
A total of 586 patients received either n-3 PUFA (n=289) or a placebo (n=297). Subjects were mean 66 years of age. Approximately 73% of subjects were enrolled because of single episode of AF that required electrical cardioversion, 63% received amiodarone, 61% received a ß-adrenergic receptor blocking drug, and more than 90% were hypertensive.

After 1 year of follow-up there was no significant difference in the primary efficacy endpoint of survival free of AF between the n-3 PUFA- and placebo-treated patients (HR, 1.28; 95% CI, 0.77 to 1.89; p=0.171; Figure 1), nor were there any significant differences regarding the other prespecified endpoints.

Figure 1. Survival Free of AF.



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According to Dr. Macchia, when the results of this study are added to those of previous studies with a similar hypothesis, the results are clearly neutral, leading to the conclusion that there is no role for n-3 PUFA in the secondary prevention of AF.

Future cardiovascular society guideline updates for the treatment of AF will likely incorporate these findings and note the lack of any benefit for preventing AF recurrence with the tested PUFA regimen and patient population. The benefits (or lack thereof) of other PUFA strategies, including natural sources from fish consumption or use in other patient populations such as lone or new-onset AF, remain unknown.

ASPIRE: Using Aspirin to Prevent Recurrence of VTE

Written by ***Rita Buckley***

Venous thrombosis, which manifests mainly as deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and serious disorder; it occurs in 1 per 1000 individuals per year worldwide, and patients who suffer from DVT or PE are at risk of recurrent events [Rosendaal FR. *PLoS Med* 2012]. There is limited information on safe and effective long-term preventive strategies. Timothy Brighton, MBBS, South Eastern Area Lab Services, Prince of Wales Hospital, Sydney, Australia, presented results from the Aspirin to Prevent Recurrent Venous Thromboembolism [ASPIRE; ACTRN12605000004662] trial.

ASPIRE was a double-blind, randomized, placebo-controlled study that evaluated the efficacy of low-dose aspirin versus placebo in preventing a recurrence of venous thromboembolism (VTE) [Brighton TA et al. *N Engl J Med* 2012]. The primary endpoint was the composite of recurrent symptomatic objectively confirmed DVT, nonfatal PE, or fatal recurrence of VTE.

A total of 822 patients aged ≥18 years were randomized to receive 100 mg/day of aspirin or placebo for up to 4 years following initial anticoagulation therapy. Inclusion criteria were completion of initial anticoagulation therapy after a first unprovoked proximal DVT and/or PE, and commencement of study medication within 6 weeks (and as soon as possible) after the end of initial anticoagulant therapy.

During a median follow-up period of 37.2 months, VTE recurred in 73 of 411 (18%) patients assigned to placebo and in 57 of 411 (14%) assigned to aspirin (6.5% per year vs 4.8% per year; HR aspirin, 0.74; 95% CI, 0.52 to 1.05; p=0.09).

Although there was no significant reduction in the primary endpoint of recurrent VTE, treatment with aspirin was associated with a lower rate of the prespecified secondary broad composite outcomes combing venous and arterial thrombotic events as well as bleeding, including the rate of VTE, myocardial infarction (MI), stroke, or cardiovascular death (HR aspirin, 0.66; 95% CI, 0.48 to 0.92); The rate of VTE, MI, stroke, major bleeding, or death from any cause was reduced by 33% (HR, 0.67; 95% CI, 0.49 to 0.91; p=0.01). There was no significant difference in the rates of major or clinically relevant nonmajor bleeding episodes (0.6%/year with placebo vs 1.1%/year with aspirin; p=0.22) or serious adverse events.

Although the primary hypothesis that aspirin would

significantly reduce the rate of recurrent VTE was not demonstrated, the presenter speculated that this may have been due to a lack of sufficient statistical power limitation. When combined with earlier data [WARFASA; Becattini CN et al. *N Engl J Med* 2012], Dr. Brighton suggested that the ASPIRE study adds to evidence that long-term, low-dose aspirin reduces the risk of recurrent VTE and major vascular events in patients with a first unprovoked VTE compared with placebo (Table 1) [Brighton TA et al. *N Engl J Med* 2012].

Table 1. Meta-analysis ASPIRE and WARFASA.

Outcome and Study	Placebo No. of Events/Total No. of Patients	Aspirin No. of Events/Total No. of Patients	HR (95% CI)	p Value	p Value for Heterogeneity
Venous thromboembolism					0.42
ASPIRE	73/411	57/411	0.74 (0.52–1.05)	0.09	
WARFASA	43/197	28/205	0.58 (0.36–0.93)	0.02	
Pooled	116/608	85/616	0.68 (0.51–0.90)	0.007	
Major vascular events					0.96
ASPIRE	88/411	62/411	0.66 (0.48–0.92)	0.01	
WARFASA	48/197	36/205	0.67 (0.43–1.03)	0.06	
Pooled	136/608	98/616	0.66 (0.51–0.86)	0.002	
Clinically relevant bleeding					0.50
ASPIRE	8/411	14/411	1.72 (0.72–4.11)	0.22	
WARFASA	4/197	4/205	0.98 (0.24–3.96)	0.97	
Pooled	12/608	18/616	1.47 (0.70–3.08)	0.31	

Adapted from Brighton TA et al. Low-Dose Aspirin for Preventing Recurrent Venous Thromboembolism. *N Engl J Med* 2012; 367:1979-1987.

Dr. Brighton said that aspirin is an effective option for patients who are unable or do not wish to continue anticoagulation beyond their initial therapy. Unlike warfarin therapy, aspirin is simple, widely available, low cost, and well tolerated, with low risks of bleeding and benefits that extend beyond the prevention of recurrent VTE.

Science Advisors' Statement

The clinical impact of these two trials should be interpreted carefully. While administration of aspirin may result in a modest reduction in VTE, trials of prolonged anticoagulant therapy—including those at reduced intensity—have shown benefit of greater magnitude [Ridker PM et al. *N Engl J Med* 2003; Schulman S et al. *N Engl J Med* 1997; Kearon C et al. *N Engl J Med* 1999; Kearon C et al. *Chest* 2012]. Clinicians should carefully consider treatment guidelines, prior data, and individual patient risks when advising patients with regard to appropriate antithrombotic therapy after VTE, and should not consider aspirin an alternative therapy with equivalent efficacy in patients with a clear indication for anticoagulation for VTE.

First Large-Scale Platelet Function Evaluation in an Acute Coronary Syndrome Trial: The Trilogy ACS-Platelet Function Substudy

Written by ***Phil Vinall***

In a platelet function substudy of A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects [TRILOGY ACS; NCT00699998] trial, patients with an acute coronary syndrome (ACS) treated with prasugrel experienced significantly lower platelet reactivity compared with patients treated with clopidogrel. However, there was no relationship between platelet reactivity and the occurrence of ischemic outcomes, nor were there significant differences in the rates of the composite endpoint of cardiovascular death, myocardial infarction (MI) and stroke, or TIMI major bleeding between the 2 treatment groups enrolled in the platelet function substudy. Paul Gurbel, MD, Sinai Hospital of Baltimore, Baltimore, Maryland, USA, presented the results of this novel mechanistic evaluation of platelet function in the TRILOGY ACS trial.

The substudy included 2564 patients enrolled in the TRILOGY ACS trial that randomized patients with unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI) initially managed medically without revascularization in the TRILOGY ACS trial to prasugrel or clopidogrel. Prasugrel was administered with dose adjustment based on weight or age: patients aged <75 years and weighing ≥60 kg received 10 mg/day, while those aged ≥75 years (regardless of weight) and those aged <75 years who weighed <60 kg received 5 mg/day. All patients in the clopidogrel group received 75 mg/day.

In the substudy group, platelet function was measured using the VerifyNow P2Y12 assay at baseline, and at 2 hours, and 1, 3, 6, 12, 18, 24, and 30 months after randomization. The primary efficacy endpoint was a composite of cardiovascular death, MI, and stroke through 30 months. Key secondary endpoints included all-cause death and MI. Approximately 20% of patients were aged ≥75 years, 39% were female, 33% had UA, and 67% had NSTEMI.

Patients treated with prasugrel (10 mg/day) had significantly ($p<0.0001$) lower P2Y12 reaction units (PRU) compared with those treated with clopidogrel, starting at 2 hours and persisting throughout the 30 month study (Figure 1). The median PRU values at 30 days were 64 (IQR 33 to 128) in the prasugrel group versus 200