Intriguingly, the XPRESS trial has shown no difference in 28-day survival of patients with severe sepsis who received Xigris with or without heparin prophylaxis, in spite of the presumably higher rate of APC inactivation with concomitant heparin. A non-inferiority study comparing enzyme and zymogen for the survival of patients with severe sepsis is urgently needed. In the mean time, a rationale exists for the administration of the zymogen in patients presenting with contraindications to APC treatment.

**PROPHYLAXIS AND TREATMENT OF THROMBOEMBOLISM II**

**HOMOCYSTEINE: STILL A RELEVANT THROMBOPHILIA MARKER?**

W. Ageno

Department of Clinical Medicine, University of Insubria, Varese, Italy

In the mid 1990s, a meta-analysis of early observational studies on the role of hyperhomocysteinemia as a risk factor for arterial vascular disease found a statistically significant association between homocysteine levels and both coronary heart disease (OR 1.7, 95% CI 1.5-1.9) and stroke (OR 2.5, 95% CI 2.0-3.0). However, most included studies were retrospective, and thus subject to bias and confounding. Although the magnitude of the association was not confirmed by subsequent pooling of data from prospective cohort studies, an association between hyperhomocysteinemia and cardiovascular disease, especially stroke, was substantially confirmed. Similar findings were reported from retrospective and prospective cohort studies investigating the association between homocysteine levels and venous thromboembolism. Whether homocysteine plays a direct causal role by promoting oxidative stress, endothelial cell damage, inflammation, and thrombosis or it is an innocent bystander remains uncertain. This is particularly true for mild hyperhomocysteinemia (generally defined as homocysteine levels of 15-30 μmol/L), which can be associated to increasing age, smoking, postmenopausal state, metabolic syndrome, sedentary lifestyle, decreased renal function, and use of different drugs. Thus, there is a chance that hyperhomocysteinemia is an epiphenomenon rather than a risk factor. A number of recent studies have investigated the impact of vitamin therapy on homocysteine levels and on cardiovascular events. Vitamin therapy was clearly effective in reducing homocysteine levels, but failed to demonstrate conclusive benefits in the secondary prevention of ischemic heart disease, cardiovascular death, or venous thromboembolism. The results on stroke were more promising, but data appear inconclusive. In all these studies patients were included and treated regardless of their baseline homocysteine levels. The efficacy of vitamin therapy in a more selected population of patients with higher baseline homocysteine levels remains to be demonstrated.

**Efficacy and Safety of Various Vitamin K Antagonists for the Treatment of Symptomatic Venous Thromboembolism**

A.W.A. Lensing, for the MATISSE investigators

Academic Medical Center, Amsterdam, the Netherlands

Introduction. Warfarin is the most widely used vitamin K antagonist (VKA). Although other VKAs are considered to have similar efficacy and safety profiles when targeted to the same INR range, evidence is lacking. We took advantage of two large multinational venous thromboembolism treatment trials to compare efficacy and safety of the different VKAs used. Methods. Treatment with a VKA was started within 72 hours and was continued for 3 months. Based
on local practice, either warfarin, acenocoumarol, phenprocoumon or fluindione was used with the dose adjusted to a target INR range between 2.0 and 3.0. The 3-month incidence of recurrent venous thromboembolism and of major bleeding observed among the VKAs was compared using Cox’s proportional hazard model, adjusted for potential confounders. Results: Among 4289 patients eligible for this analysis, 142 venous thromboembolic events occurred for 3-months incidences of 4.6% for warfarin, 2.5% for acenocoumarol, 2.1% for phenprocoumon, and 2.9% for fluindione, for adjusted hazard ratios versus warfarin of 0.56 (95% CI, 0.35 to 0.87), 0.49 (95% CI, 0.23 to 1.05), and 0.61 (95% CI, 0.28 to 1.31), respectively. A total of 71 major bleeds occurred, for 3-month incidences of 2.2% with warfarin, 1.8% with acenocoumarol, 0.3% with phenprocoumon, and 1.2% with fluindione, for adjusted hazard ratios versus warfarin of 0.84 (95% CI, 0.48 to 1.5), 0.15 (95% CI, 0.02 to 1.1), and 0.54 (95% CI, 0.17 to 1.7), respectively. The frequency of INR monitoring was similar for the four VKA groups. Conclusions: Acenocoumarol, phenprocoumon and fluindione seem to be at least as effective and safe as warfarin in patients with venous thromboembolism. However, the presumption that all vitamin K antagonists are clinically equivalent might not be true since in our study at least one VKA was observed to be more effective than warfarin. Given the millions of patients exposed to various VKAs world-wide, further exploration of our findings by clinical trials is likely to have important public health implications.