EFFECT OF ANTICOAGULANT TREATMENT WITH RA-233 (MOPIDAMOLE) ON SURVIVAL IN BRONCHIAL CANCER. B. Schneider (1), C. Geser (2), W. Feuerer (2). Institute for Biometrics, Medizinische Hochschule Hannover, Germany (1), Dr. Karl Thomae GmbH, Medical Division, Biberach on der Riß, Germany (2).

RA-233 (mopidamole) is a phosphodiesterase inhibitor that has been shown previously to limit progression of malignancy in certain experimental animal models and in pilot studies in humans. To test its therapeutic effect a multicenter double blind controlled clinical trial was performed from 1982-1986 with patients suffering from (non small-cell) bronchial cancer, 7 centers participated and the data of 270 patients (147 treated with placebo and 123 with RA-233) could be analyzed. Median treatment time was 18 months, median observation time 21 months. With RA-233 treatment survival could be increased significantly (Savage test, p < 0.05 one sided) compared to placebo treatment (mean survival time in the RA-233 group 1080 days, in the placebo group 960 days). Cox-analysis showed a significant reduction of the hazard function to 0.6 by RA-233 treatment compared with placebo. As additional significant influence factors of the hazard function, the postsurgical TNM-class and the histological type could be revealed. Patients from stage T1 or T2 and N0 survived significantly longer than patients with other TNM-stages. There is no interaction between treatment and TNM-class; i.e. RA-233 effect is in all TNM-stages similar. In contrast to survival metastasis-frequency and metastasis-free interval could not be influenced by RA-233.

DIRECT STIMULATION OF Ca2+-ACTIVATED HUMAN PLATELET PHOSPHOLIPASE A2 BY DIACLYGLYCEROL. D. Deykin and R. M. Kramer. Boston VA Medical Center and Boston University School of Medicine, Boston, MA, U.S.A.

These studies examined the effect of diacylglycerol on Ca2+-dependent phospholipase A2 from human platelets. Phospholipase A2 was solubilized and partially purified to a stable form in the presence of polyethylene glycol and an enzymatic activity determined using sonicated arachidonoyl phosphatidylcholine (PC) as substrate. (Kramer RM, et al: RBA 579:394, 1986) Phospholipase A2 activity was increased when diacylglycerol was incorporated into the substrate arachidonoyl-PC. In the presence of 1 mM (29 mol %) 1,2-diacylglycerol the enzymatic activity was stimulated 3.6-fold. Exogenously added sn-1,2-diacylglycerol also enhanced phospholipase A2 activity, producing a maximal stimulation of 4.6-fold at a concentration of 25 mM. Comparative studies conducted with pancreatic, bee-venom and snake venom phospholipase A2 showed that the activity of these extracellular phospholipases towards the arachidonoyl-PC substrate was also increased by diacylglycerol, but the stimulation was less than observed for platelet phospholipase A2. We conclude that in stimulated platelets Ca2+-activated phospholipase A2 may be regulated by newly generated diacylglycerols, not only via protein kinase C-mediated events, but also directly through conformational changes imposed by the diglycerides on cellular membrane phospholipids.

REGULATION OF PLATELET RECEPTORS FOR FIBRINOGEN AND VON WILLEBRAND FACTOR BY PROTEIN KINASE C. Sheila Timmons and Jack Hawiger. New England Deaconess Hospital and Harvard Medical School, Boston, MA. 02215, USA.

Positive and negative regulation of platelet receptors for adhesive proteins, fibrinogen (F) and von Willebrand factor (VWF) determines whether binding of these ligands will or will not take place. We have shown that diacylglycerol and cyclic AMP inhibits binding of F and VWF to human platelets. Now we show that positive regulation of F and VWF binding to platelets via the glycoprotein IIb/IIIa complex is dependent on platelet protein Kinase C, a calcium- and phospholipid-dependent enzyme. A potent activator of Protein Kinase C, phorbol-12-myristoyl-13-acetate (PMA) induced saturable and specific binding of F and VWF which was inhibited by synthetic peptides, gamma chain dodecapeptide (gamma 400-411) and RGDS. The phosphorylation of 47Kda protein (P47), a marker of Protein Kinase C activation in platelets, preceded binding of F and VWF induced with PMA as well as with ADP and thrombin. Sphingosine, an inhibitor of Protein Kinase C, blocked binding of F and VWF to platelets stimulated with PMA, ADP, and thrombin. Inhibition of binding was concentration-dependent and it was accompanied by inhibition of platelet aggregation. Thus, stimulation of Protein Kinase C is required for exposure of platelet receptors for adhesive proteins whereas inhibition of Protein Kinase C prevents receptor exposure. Protein Kinase C fulfills the role of an intraplatelet signal transducer, regulating receptors for adhesive proteins, and constitutes a target for pharmacologic modulation of the adhesive interactions of platelets.