CONTROLLED TRIAL OF SULFINPYRAZONE IN RHEUMATIC HEART DISEASE. PRELIMINARY RESULTS. Peter Steele, Joseph Rainwater, Edward Genton. Denver Veterans Administration Hospital, University of Colorado Medical Center, Denver, Colorado.

Platelet survival time (SURV) has correlated with a history of thromboembolism (TE) in patients with rheumatic heart disease (RHD). A controlled trial of sulfinpyrazone (SFP) in RHD is in progress and 138 patients have been entered. SURV ($^{51}\text{Chromium}$ labelling) was shortened (2.3 ± 0.08 days; AVE $t\ 1/2 \pm \text{SEM}$; normal 3.7 ± 0.04 days) in 40 of 41 (98%) with a history of TE and in 76 of 97 (78%) (2.9 ± 0.07 days; $P < 0.001$) of those without a history of TE. One hundred sixteen with shortened SURV have been randomized to SFP or placebo and 67 have either completed four years ($N=37$), undergone mitral valve replacement ($N=18$) (ave 19 months; range 6-32 months), had definite TE ($N=8$) (average 14 months; range 8-23 months) or died ($N=4$) (average 15 months; range 5-22 months). Definite TE (prolonged neurologic deficit) occurred in one on SFP and in seven on placebo (all with shortened SURV) ($\chi^2 = 4.31$; NS). SFP increased SURV (2.4 ± 0.12 to 2.7 ± 0.13 days; $N=23$; $P < 0.001$) and 12 (52%) had an increase in SURV of > 0.02 days. The patient on SFP with new TE had no change in SURV (2.3 to 2.3 days). Placebo did not alter SURV (2.4 ± 0.15 to 2.5 ± 0.08 days; $N=26$; NS) and two (8%) had an alteration of SURV by > 0.02 days. SURV was not altered in patients with normal SURV (3.7 ± 0.08 to 3.6 ± 0.08 days; $N=12$; NS) and no patient with normal SURV has had shortened SURV on subsequent yearly measurement. Patients with normal SURV were not randomized. Results suggest that SURV is shortened in patients with RHD who have had or will have TE, that SFP increases SURV and may prevent TE in these patients.

THE ANTI-THROMBOTIC POTENTIAL OF DIHOMO- γ -LINOLENIC ACID. P.B.A. Kernoff, J.A. Davies and G.P. McNicol. University Department of Medicine, The General Infirmary, Leeds, England; A.L. Willis and K.J. Stone. Roche Products Limited, Welwyn Garden City, England.

Dihomo- γ -linolenic acid (DHLA; Ro 12-1989, Roche), a natural precursor of prostaglandin E_1 , has been evaluated as a potential antithrombotic agent by studying its effects on platelet function, blood coagulation and blood viscosity. In vitro investigations were performed on blood obtained from 10 normal subjects and 10 patients with diabetes mellitus, 8 of whom had evidence of severe microangiopathy. Prior incubation of normal platelets with DHLA caused a marked and dose-related inhibition of : platelet aggregation in response to stimulation with AIP, collagen, epinephrine, thrombin and ristocetin; platelet glass-bead retention; release of serotonin and platelet factors 3 and 4. Effects on diabetic platelets were less marked but still highly significant. DHLA also reversed platelet aggregation and inhibited the adhesion of porcine platelets to collagen-coated glass. No significant effects were found on whole-blood viscosity or tests of blood coagulation apart from a slight shortening of the one-stage prothrombin time. Ex vivo studies were performed on 3 normal volunteers after oral administration of single doses of DHLA. Increased plasma DHLA/arachidonic acid ratios resulted in all instances (Stone et al, this meeting). No adverse effects were noted but consistent evidence of a favourable change in haemostatic tests was not obtained. The spectrum of in vitro inhibitory activity of DHLA on platelets is wider than that reported for other potential anti-thrombotic agents and our results suggest that DHLA shows considerable promise in this respect.

DOSE-DEPENDENT INHIBITION OF EXPERIMENTAL ARTERIAL THROMBOSIS BY CARBENICILLIN AND TICARCILLIN. B.T. Lyman, G.J. Johnson and J.G. White. V.A. Hospital and U. of Minn., Minneapolis, MN, USA.

Drugs that inhibit platelet (PL) function may be useful in the prophylaxis of arterial thrombosis. We have shown that carbenicillin (CARB) and ticarcillin (TIC) cause dose-dependent inhibition of PL aggregation (AGG) in dogs, and that high doses of either of these penicillins significantly decrease the frequency of thrombosis in pronase (PN) injected arteries of dogs. Using this model we have compared the thrombosis prophylaxis effectiveness of these penicillins administered in low dose (250mg/Kg/24 hr , s.c.) (LD-P) versus high dose (750mg/Kg/24 hr , s.c.) (HD-P). Treatment for 3 to 7 days with LD-P resulted in marked inhibition of ADP-induced AGG, but had little or no effect on collagen-induced AGG, while HD-P routinely inhibited collagen as well as ADP-induced AGG. Control dogs were untreated, and their PL function remained normal. Thrombosis with total occlusion occurred in 13 of 15 arteries in control dogs, while only 3 of 29 segments totally occluded in HD-P treated dogs ($\chi^2 = 21.7$; $p < 0.001$). However, total occlusion developed in 13 of 20 arteries in dogs receiving LD-P ($\chi^2 = 1.1$; $p < 0.3$). The frequency of occlusion was significantly lower ($p < 0.001$) following treatment with HD-P than LD-P. Aspirin (ASA) administration in low dose (650mg/24 hr p.o.) (LD-A) or high dose (2600mg/24 hr p.o.) (HD-A) uniformly inhibited collagen-induced PL AGG, but total occlusion developed in 11 of 16 PN injected arteries in dogs given LD-A, and in 10 of 12 arteries in dogs given HD-A. We conclude that CARB and TIC are effective experimental antithrombotic agents. Their effect is dose-dependent and closely correlated with inhibition of collagen-induced PL AGG. In high doses CARB and TIC are more effective than ASA in preventing PN induced arterial thrombosis. CARB and TIC warrant further study as potentially useful antithrombotic agents in humans.