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Anticoagulation with warfarin downregulates inflammation

P. S. MACLEAN, R. C. TAIT, A. RUMLEY,* A. D. MCMAHON† and G. D. LOWE*

*Department of Haematology and *University Department of Medicine, Royal Infirmary, and †Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK*

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Dear Sir

It is now apparent that a dynamic interaction may exist between the two processes of coagulation and inflammation. There is considerable evidence supporting a role for inflammation predisposing to blood clotting [1,2]. However, this study investigates the possibility that the coagulation system can directly effect regulation of inflammation.

We have previously demonstrated, in an epidemiological study, that D-dimer and C-reactive protein (CRP) are correlated, and postulated that fibrin turnover (as measured by D-dimer) may be a determinant of inflammation and CRP in the population [3]. Roumen-Klappe *et al*. suggested that a rise in CRP shown during the acute phase of deep vein thrombosis (DVT) is a direct result of the thrombotic event rather than a causative factor [4], and *in vitro* studies by Robson *et al*. have demonstrated that fibrin degradation products including D-dimer have the effect of increasing production and secretion of the inflammatory mediators interleukin (IL)-1 and IL-6 from monocytes [5]. These studies suggest that increased turnover within the

Table 1 Summary of Results

		Median	Mean change from baseline	Lower 95% CI for mean change	Upper 95% CI for mean change	*P*
INR	Day 0	0.9	–			
	Day 15	2.4	+1.67	+1.23	+2.1	<0.001
	Day 29	2.2	+1.57	+0.97	+2.16	<0.001
D-dimer	Day 0	58	–			
($ng\,mL^{-1}$)	Day 15	33	−49.07	−76.61	−21.53	0.002
	Day 29	39	−30.73	−62.63	+1.17	0.058
CRP	Day 0	2.3	–			
($mg\,L^{-1}$)	Day 15	0.8	−1.97	−3.83	−0.12	0.038
	Day 29	1.4	−0.15	−2.90	+2.16	0.909
IL-6	Day 0	2.9	–			
($pg\,mL^{-1}$)	Day 15	1.6	−0.84	−1.70	+0.01	0.053
	Day 29	2.8	−0.04	−0.99	+0.92	0.931

Correspondence: Peter Maclean, Department of Haematology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK.
E-mail: petermaclean@btopenworld.com

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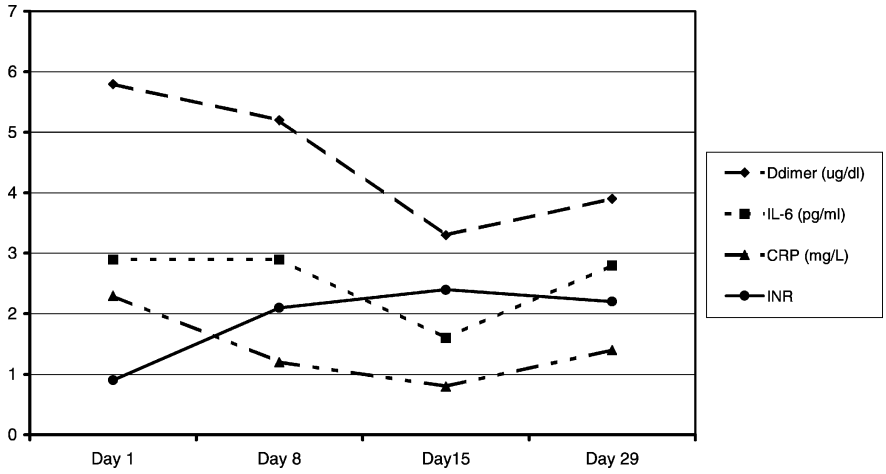

Fig. 1. Comparative median values of INR, D-dimer, CRP and IL-6.

coagulation system could effect upregulation of the inflammatory system. Conversely, Downing *et al*. have shown that low-dose low molecular weight heparins (LMWH) possesses anti-inflammatory properties distinct from its anticoagulant properties [6].

The aim of our study was to determine whether down-regulation of inflammation might also be achieved by oral anticoagulation, as a result of reduced activation of coagulation.

The study subjects consisted of 15 patients (10 male, five female; mean age 61 years, range 48–75 years) referred for elective outpatient anticoagulation for stroke prophylaxis. None had any history of recent thromboembolic events. All were commenced on Warfarin using a standardized 5-mg loading regime with venous International Normalized Ratio (INR) checked at day 5, then at weeks 1, 2, and 4 [7].

Citrated plasma samples were either processed immediately (INR) or stored in 1-mL aliquots at -70°C until analysis. INR was assessed using Manchester PT Reagent on an AMAX CS-190. CRP was assayed using a high-sensitivity assay on the Prospec Nephelometer (Dade Behring, Liederbach, Germany). ELISA was used to measure D-dimer (Biopool AB, Umea, Sweden) and IL-6 (R&D System Europe, Abington, UK).

Changes in parameter value from baseline were calculated and assessed using Student's *t*-test.

Our results demonstrate at day 15 a mean reduction of $49.07\,\mathrm{ng\,mL^{-1}}$ (95% confidence interval -76.61, -21.53) in D-dimer and $1.97\,\mathrm{mg\,L^{-1}}$ (95% CI -3.83, -0.12) in CRP levels, $P < 0.05$ in both cases. Mean reduction in IL-6 was also shown but not reaching significance ($P = 0.053$). It should be noted that IL-6 levels would have reached significance if those patients failing to reach target INR were excluded. By day 29 the fall in CRP from baseline failed to reach significance.

We confirmed reduction in D-dimer after warfarinization of atrial fibrillation patients to a target INR of 2–3. We also showed for the first time reductions in CRP and IL-6 after 15 days of warfarin, consistent with our hypothesis that coagulation activation products (e.g. D-dimer) are proinflammatory. At day 29 INR was less well controlled and reductions in D-dimer, CRP and IL-6 were no longer statistically significant. This suggests that an adequate level of warfarinization may be required for its anti-inflammatory effect. Although this study is small it does illustrate parallel trends in the activity within the systems of coagulation and inflammation which warrant further investigation in larger studies.

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