Letters to the Editor

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Effect of Chronic Angiotensin II Type I Receptor Antagonism and Angiotensin Converting Enzyme Inhibition on Plasma Fibrinolytic Variables in Patients with Heart Failure

Dear Sir,

A number of studies have attempted to examine the interaction between the renin-angiotensin-system (RAS) and the fibrinolytic system, especially the effect of angiotensin converting enzyme (ACE) inhibition on plasma markers of endogenous fibrinolysis (1-13). Four were completely “negative” (3, 8, 10, 12) and nine were partly “positive” (1, 2, 4-7, 9, 11, 13). None showed any increase in any of these variables, and so the established view is that ACE inhibitors tend to decrease some or all of these variables. Two studies compared an ACE inhibitor with an angiotensin II type I (AT1) antagonist (6, 9). The first (in heart failure) showed that a single dose of losartan reduced PAI-1 antigen more than enalapril (6). The second (in normals) showed that 2 weeks of quinapril reduced PAI-1 activity and antigen, and that 2 weeks of losartan reduced t-PA antigen (9). We wanted to compare the effects of ACE inhibition and AT1 antagonism on endogenous fibrinolysis in patients with heart failure over a longer period. We randomised patients with heart failure to double-blind cross-over treatment with an ACE inhibitor and an AT1 antagonist (5 weeks each) and measured the effect on plasma PAI-1 activity, t-PA antigen, fibrin D-dimer and von Willebrand factor.

The study was conducted with the approval of the local Ethics Committee and all patients gave written informed consent. Twelve patients with chronic heart failure secondary to left ventricular systolic dysfunc-
tion confirmed by echocardiography were studied. All medications apart from ACE inhibitor/AT1 antagonist were constant throughout the period of study. Patients were randomised to double-blind cross-over treatment with enalapril 10 mg bd for 5 weeks followed immediately by losartan 25 mg bd for 5 weeks, or vice versa. At the end of each 5 weeks patients attended for study, having abstained from all aspirin therapy for 14 days. Patients took all their other usual medication including study treatment at 8 am before attendance on the day of study at 2 pm. After resting supine for 20 min, 10 ml of blood was drawn, collected into EDTA tubes, kept on ice, centrifuged at 2000 G for 20 min at 4°C, platelet-free plasma was aliquotted and stored at -80°C before assay. All results were expressed as mean values with standard errors. All results were compared using two-tailed paired t tests. Differences were considered statistically significant at a value of p < .05.

Plasma fibrinolytic variables are shown in Fig. 1. There was no signif-
ificant difference in any of the fibrinolytic variables studied between the two study days, and all were within the normal range. In particular, mean PAI-1 activity was indistinguishable between the two study days, and indeed, extremely close to 100% of the normal pool (99 ± 7% on the enalapril day, 101 ± 8% on the losartan day).

We have shown no difference in plasma markers of endogenous fibrinolysis or vWF, after 5 weeks of treatment with enalapril 10 mg bd and after 5 weeks of losartan 25 mg bd, in patients with heart failure. In particular, we have failed to show any difference whatsoever in PAI-1 activity. These findings contrast with the previous reports that losartan reduces PAI-1 antigen more than enalapril in patients with heart failure (6), and that quinapril reduces PAI-1 levels but losartan reduces t-PA antigen levels (9). If acute AT1 antagonism reduces PAI-1 more than acute ACE inhibition, it might be anticipated that chronic AT1 antagonism would also reduce PAI-1 more than chronic ACE inhibition. There was no difference in our study. It is impossible to say whether this was because the ACE inhibitor and the AT1 antagonist were equally effective, or because they were equally ineffective. If their acute effects were as previously demonstrated, it is impossible to say whether with chronic ACE inhibition PAI-1 falls, or with chronic AT1 antagonism PAI-1 levels rise. It suggests that there is a distinction to be made between the acute and chronic effects of AT1 antagonism and ACE inhibition, i.e., that this discrepancy may not be as surprising as it at first appears. Whereas we used enalapril 20 mg a day and losartan 50 mg a day, the previous study used a single dose of enalapril 10 mg and losartan 50 mg (6). It is possible that the difference between losartan and enalapril shown in the previous trial is dose-dependent. It is not surprising that a study comparing a similar dose of losartan with a different dose of enalapril has given a different result. It is interesting that a study comparing the effects of a very large dose of quinapril with double the dose of losartan found differences of debatable significance between them (9). It is important that the message that AT1 antagonism has more beneficial effects on endogenous fibrinolysis than ACE inhibition does not go uncontradicted.

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Fig. 1 Effect of enalapril and losartan on plasma fibrinolytic parameters

Dear Sir,

Venous thromboembolism is a recognized complication of malignancy. In even the absence of clinically evident thrombotic disease, cancer patients commonly have laboratory signs of coagulation activation. The biologic significance of this activation in cancer patients is not clear, but experimental and pathological studies have indicated that the hemostatic system plays a crucial role in cancer spread (1). Hence, it has been postulated that anticoagulant agents, such as vitamin K-antagonists (VKA) and heparins, may limit progression of malignancy. Indeed, various experimental studies have shown that tumor growth and metastasis can be inhibited by anticoagulants (1, 2). However, it is still a matter of debate whether anticoagulant treatment also affects cancer progression in man. Recently, a lower incidence of newly diagnosed malignancy was evaluated before analysis. Only properly randomized studies, in which the study groups were treated equally besides the VKA intervention and in which dosage and duration was specified, were included. The authors were contacted when potentially eligible studies reported incomplete data. One year total-mortality rates were extracted and odds ratios (OR) for patients treated with VKA or placebo/no (additional) treatment were calculated separately for each study and then pooled using the Mantel-Haenszel method. A statistical test of homogeneity was used to decide whether trials could be combined (4).

The search identified 18 articles, but only 5 fulfilled the inclusion criteria (5-9). All other investigations were excluded from further analysis because they were non-randomized or cohort studies, lacked appropriate control groups, i.e. the study groups were not equally treated besides the VKA intervention and in which dosage and duration was specified, were included. The authors were contacted when potentially eligible studies reported incomplete data. One year total-mortality rates were extracted and odds ratios (OR) for patients treated with VKA or placebo/no (additional) treatment were calculated separately for each study and then pooled using the Mantel-Haenszel method. A statistical test of homogeneity was used to decide whether trials could be combined (4).

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The Effects of Vitamin K-antagonists on Survival of Patients with Malignancy: A Systematic Analysis

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