Table 1. Alelle frequencies of HR2 haplotype and factor V Leiden in patients and control subjects.

	Patients n (%)	*Controls n (%)*	*OR (95% CI)*
HR2	14 (12.17)	20 (17.39)	0.57 (0.22–1.45)
FV Leiden	8 (6.96)	2 (1.74)	4.00 (0.79–27.33)
HR2 + FV Leiden	1 (0.87)	0	–

thromboembolism (VTE) has been previously studied. Although the results are controversial, double heterozygotes for HR2 and FV Leiden seem to have an increased risk of VTE due to a synergistic action between both polymorphisms.[8] In another previous report no relationship between the HR2 haplotype and the risk for myocardial infarction was found.[9] To our knowledge, no study aimed at analyzing the HR2 haplotype as a predisposing factor for CVD has been published so far.

According to our results, the HR2 haplotype does not seem to play any role as a risk factor for CVD. Although the number of subjects included in this study is relatively small, both groups, patients and controls, were homogeneous, which reduces the probability of bias.

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Safety and effectiveness of low-dose, oral vitamin K1 administration in asymptomatic out-patients on warfarin or acenocoumarol with excessive anticoagulation

The management of asymptomatic overanticoagulation with low dose vitamin K1 is recommended in patients taking oral anticoagulants, independently of the type of coumarin being administered. To evaluate the safety and effectiveness of this practice we observed 127 patients on warfarin and 14 on acenocoumarol, who received 2 mg oral vitamin K1 on at least one occasion. At the first measurement, international normalized ratio (INR) mean values were significantly lower in patients on acenocoumarol than in patients on warfarin (p=0.0001) and all patients on acenocoumarol showed INR values below the therapeutic range. Vitamin K1 should be used cautiously in patients being anticoagulated with acenocoumarol.

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The major adverse event of oral anticoagulant therapy (OAT) is bleeding and its risk increases with INR levels. The optimal management of outpatients with asymptomatic elevation of INR remains debatable. Coumarin withdrawal with or without administration of a low dose of oral vitamin K1 is commonly suggested. Previous *ad hoc* studies reported rapid reversal of asymptomatic overanticoagulation with low dose vitamin K1 administration, without subsequent coumarin resistance in patients treated with warfarin.[1] On the basis of these results Scientific Societies recommended this practice for OAT patients independently of the drug administered.[2-3] However, few data are available on patients treated with acenocoumarol.[4]

In our Anticoagulation Clinic the routine treatment of asymptomatic overanticoagulation is temporary suspension of OAT (for one day) and low dose (2 mg) vitamin K1 oral administration. The aim of our study was to evaluate the safety and effectiveness of this protocol in patients treated with warfarin and acenocoumarol.

From June 1995 to December 2001 in Florence University Hospital Anticoagulation Clinic, we prospectively followed up 1068 patients for a total period of 2329 patient/years: 1021 were receiving warfarin (2254 patient/years) and 47 were receiving acenocoumarol (75 patient/years). The indications for OAT were: heart valve prostheses 23%, venous thromboembolism 27%, atrial fibrillation 28%, ischemic heart disease 8.5%, arterial vascular disease 7%, heart valve disease 6%, other 0.5%. In all patients with asymptomatic overanti-

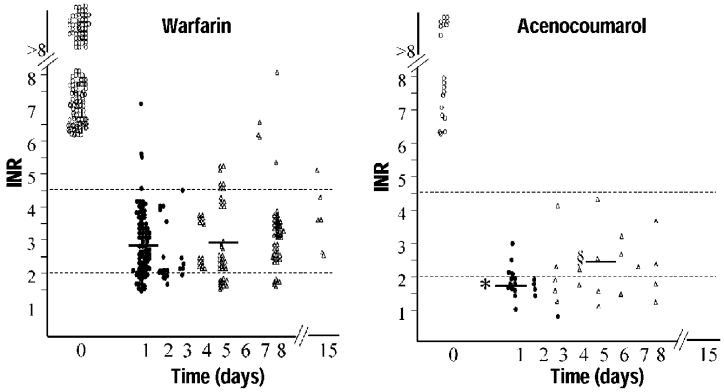

Figure 1. INR values before and after vitamin K administration.
°INR level before vitamin K1 administration (TO);
• INR level 1-3 days after vitamin K1 administration (T1);
△INR level 4-15 days after vitamin K1 administration (T2);
***p=0.0001 vs INR mean value of patients on warfarin;**
§p=0.05 vs INR mean value of patients on warfarin.

coagulation, OAT was stopped for one day. If the INR was over 7, 2 mg oral vitamin K1 (Konakion, Roche®) were also administered, according to the recommendations of the *Italian Federation of Anticoagulation Clinics* (FCSA).[3] Vitamin K1 was also administered to patients with an expected high risk of bleeding or in patients older than 75 years, if the INR was higher than 6. During the study period, 141 patients (127 on warfarin and 14 on acenocoumarol) received 2 mg oral vitamin K1 on 185 occasions for asymptomatic overanticoagulation. Thirty-one patients needed repeated vitamin K1 administrations during follow-up. Repeated vitamin K administration occurred at intervals ranging from 1 day to more than 3 years (mean 206.5±198 days). Twenty-six patients were on warfarin and 5 on acenocoumarol. The risk of episodic asymptomatic overanticoagulation was higher in patients receiving acenocoumarol than in those receiving warfarin. This difference was statistically significant (p<0.003). The mean interval between vitamin K1 administration (T0) and the first INR measurement (T1) was 1.5 days (range 1-3 days). The subsequent INR measurement (T2) was carried out 4-15 days later (mean 5.5 days). The occurrence of all types of bleeding and thromboembolic complications was recorded.

The mean INR values at T1 were 1.7±0.5 in patients treated with acenocoumarol and 2.9±0.9 in patients treated with warfarin (p=0.0001). The mean INR values at T2 were 2.4±0.9 in patients treated with acenocoumarol and 3.0±1.1 in patients treated with warfarin (p=0.05) (Figure 1).

The quality of anticoagulation achieved was measured using Rosendaal's method.[5] The time spent below, within, and above the intended therapeutic range was 22%, 60% and 18%, respectively, in patients never requiring vitamin K administration and 20%, 63% and 17% in patients requiring vitamin K administration. This difference was not statistically significant. The percentages of time spent with INR values below, within, and above the INR therapeutic range at T1 and T2 in the group of patients on warfarin who received vitamin K1 were not different from those observed in patients never requiring vitamin K. In contrast, all patients treated with acenocoumarol showed INR values below the therapeutic range at T1, and these values were still below the therapeutic range at T2 in 68% of cases.

During the three months before and the three months after vitamin K1 administration no major bleeding or major thrombotic complications were recorded. One patient died of renal failure 2 weeks after vitamin K1 administration. During follow-up we observed 5 minor bleeding events temporarily related to elevated INR levels that had required vitamin K1 administration (4 in patients on warfarin and 1 on acenocoumarol).

These results suggest that reversal of overanticoagulation with oral administration of 2 mg vitamin K1 in asymptomatic patients on treatment with warfarin is safe and does not cause coumarin resistance. In contrast, patients on acenocoumarol who received vitamin K 1 were exposed to under-anticoagulation. This conclusion is based on a limited number of patients who were receiving acenocoumarol, but is reasonable given the pharmacokinetic characteristics of this drug.

Our findings confirm that low-dose vitamin K1 administration can be recommended as routine practice for the management of patients treated with warfarin who develop excessive anticoagulation, but that such a strategy should be used cautiously in patients treated with acenocoumarol. Our observation prompts the need for larger studies to establish the optimal management of overanticoagulation in patients receiving acenocoumarol.

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