INR variability in anticoagulation with acenocoumarol: is it useful for identifying patients at risk of bleeding and thrombosis?

Sir,

Monitoring variability (σ) is useful for assessing anticoagulation quality in patients taking warfarin.[1,2] INR variability measures the deviation of INR from the intended range over time and is based on the hypothesis that patient's prothrombin time fluctuates all the time and in response to several factors.[3] Its value in acenocoumarol has not been studied. The anticoagulation, in terms of embolic and hemorrhagic events, quality and stability, achieved by both drugs is similar.[4-6] Since acenocoumarol has a shorter half life (8 hours), its variability values might be different.

We determined INR variability in 810 patients treated with acenocoumarol and its value as a risk indicator for thromboembolism and major hemorrhage. Patients' characteristics are given in Table 1. Fatal episodes, those requiring transfusion, hospitalization and gastrointestinal or CNS hemorrhage were defined as major bleeding.

The study was retrospective, performed on clinical and computerized archives (27,321 INR determinations in Rosendaal's program).[7] The variability of the follow-up was calculated: $\sigma^2=1/(n-1)\sum^{n}_{i=2}(INR_i-INR_{target})^2/\tau_i$; where n is the number of INR measurements and ti is time between them (in weeks). Data obtained were plotted as a histogram; the values of 25, 50 and 75 quartiles were defined as low, moderate and high variability (0.55, 0.79 and 1.12, respectively). The odds ratio of each quartile was calculated. The variability of the two tests prior to the bleeding or embolic event was measured. A group of stable patients (n=60) without complications was used as reference. We observed 47 major hemorrhages (n=47) and 22 embolisms (n=22). Three embolisms were excluded because they occurred during bacterial endocarditis and heparin therapy. The INR before the event was available in 25/47 hemorrhages (12 above, 10 below range) and 12/19 embolisms (6 below, 3 above).

Variability values are shown in Table 2. Patients with values within the 75th percentile had more complications than patients with lower values (p=0.0315) due to an increasing risk of hemorrhage. The bleeding event rate in each quartile was 1.00, 2.31 and 3.14, respectively (p=0.0304). Six patients with embolic events had a variability greater than 1.12 (not significant). Two months before the hemorrhage the variability increased in all patients but this change was not significant (p=0.2). Seventeen patients (89%) with embolism had had a mechanical heart valve replacement. Three patients (1 mitral and 2 aortic valves) had both hemorrhagic and embolic events; all of them had an underlying disease. Their variability was not greater than that observed in the other patients.

It seems that monitoring INR variability is more useful for detecting patients at risk of hemorrhagic than those at risk of embolic complications. The ISCOAT study (patients with warfarin and acenocoumarol) concluded that erratic anticoagulation might explain bleeding events at low anticoagulation intensity.[8] This observation correlates with our findings. Since anticoagulation (regardless of antiplatelet therapy) does not avoid all thromboembolic complications, other mechanisms not modified by coumarins were postulated: activation of leukocytes[9] and complement,[10] high shear stress, and other hemostatic factors.

In conclusion, monitoring INR variability can help to identify patients at risk of bleeding during treatment with acenocoumarol.

Table 1. Patients' characteristics.

Patients characteristics	
Age (years)	
Median	58.5
Range	5-88
Sex (n)	
Female	369
Male	441
Follow up	
Median (months)	30
Total (years)	1963.26
Type of disease (n)	
MHVR	384
AF/CM	348
Others	272

MHVR: mechanical heart valve replacement; AF: atrial fibrillation; CM: cardiomyopathy. Others: deep vein thrombosis/pulmonary embolism; valvular heart disease.

Table 2. Variability values.

	n	Median variabilty (SD)
Study population	810	0.93 (0.58)
Stable patients	60	0.35 (0.15)
Patients with hemorrhage	37	1.04 (0.74)
Patients with embolism	19	0.93 (0.39)

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Key words

Anticoagulation with acenocoumarol, INR variability, bleeding and embolic complications.

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The frequency of allele α^{LELY}, a low expression allele of the gene encoding erythroid spectrin α-chain, in the Greek population

Sir,

α^{LELY}, a low expression allele of the *SPTA1* gene, encodes the α-chain of erythroid spectrin.[1] It is characterized by a C→G mutation at position α1857 in exon 40;[2] it is functionally neutral, but yields major peptide map abnormalities,[3] and a C→T (nt12) mutation in intron 45. This second mutation is responsible for the partial skipping of exon 46,[4] which is essential for the nucleation of spectrin α/β-chain dimerization. Although α^{LELY} does not cause symptoms in either heterozygotes or homozygotes, it enhances the expression of deleterious α-alleles and, thus, has clinical importance.

Allele α^{LELY} is encountered in distinct ethnic groups, Caucasians, African Blacks, Japanese, Chinese, Brazilians and Parakana Indians, with a rather uniform frequency.[5,6] Among French Caucasians its frequency was estimated to be 0.31.

We investigated 175 individuals randomly selected from all parts of Greece. Exon 40 and intron 45 mutations were screened using a polymerase chain reaction.[5] Chi-square test was used to determine whether frequencies in certain groups were significantly dif-

Table 1. Statistical analysis of the frequencies of allele α^{LELY} between distinct ethnic groups considered by pairs (Caucasians (Greek + French)) vs. non-Caucasians.

	*Caucasians*Blacks*	*Africans*	*Japanese*	*Chinese*	*Brazilians*	*Parakana Indians*
n	454	86	100	36	108	82
u	0.289	0.209	0.20	0.222	0.241	0.159
Caucasians*[a]		nsd	nsd	nsd	nsd	sd
African Blacks[b]			nsd	nsd	nsd	nsd
Japanese[b]				ns	nsd	nsd
Chinese[b]					nsd	nsd
Brazilians[c]						nsd
Parakana Indians[c]						

**Greek + French Caucasians. [a]Marechal et al. 1995, and this work. [b]Marechal et al., 1995. [c]Basseres et al., 1998.*
Abbreviations: n: numbers of SPTA1 alleles investigated; Σn = 866. u: frequencies of allele α^{LELY} in individual populations. The frequencies of allele α^{LELY} were significantly different (s.d.) or not significantly different (n.s.d.) at p<0.05 between any particular pair of groups.

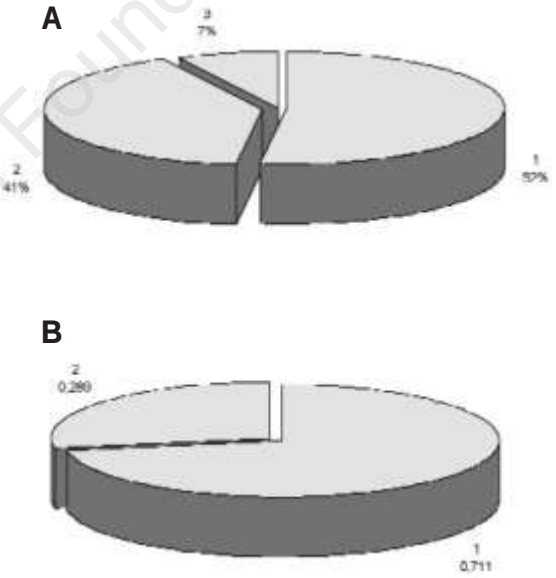

Figure 1. The allelic distribution of α/α (1), α/α^{LELY} (2) and $\alpha^{LELY}/\alpha^{LELY}$ (3) in the Greek population (A: values as percentages) and of the α (1) and α^{LELY} alleles (2) (B: values as frequencies).