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Table 1. Kaplan-Meier Estimates for Survival According to First CR Duration

	Estimates for Survival of Patients Achieving Second CR				Estimates for Survival of Patients Not Achieving Second CR				*P* Value	
	No	12 mo	18 mo	24 mo	No	12 mo	18 mo	24 mo	Log-rank	Gehan
All patients	61	.53 ± .07	.28 ± .06	.12 ± .05	127	.14 ± .03	.08 ± .03	0	<.001	<.001
>24 mo*	17	.73 ± .12	.44 ± .13	.29 ± .12	2	—	—	—	—	—
12-24 mo*	22	.73 ± .10	.30 ± .11	.18 ± .09	22	.27 ± .10	.21 ± .10	.21 ± .10	.16	.004
<12 mo*†	22	.17 ± .09	.06 ± .05	0	103	.11 ± .03	.05 ± .02	0	.14	.04

*Duration of first CR.
†Includes primary refractory patients.

analyzed data from 326 such patients seen here between 1990 and 1998. Patients with acute promyelocytic leukemia and patients given an allogeneic or autologous transplant either to induce CR or as postremission therapy were excluded. Eighty-five percent of the patients had received HDAC (≥1 g/m^2 per dose) at diagnosis or in first CR. First salvage therapy consisted of known active regimens in 76% (HDAC 55%, others 21%) and investigational single agents, often in a phase I trial, in 24%. In CR (standard definition), patients continued to receive their salvage induction regimen at reduced dose for 6 months or until recurrence, whichever came first. At recurrence, 64% of the patients received a second salvage attempt, which produced CR in 15%. Sixty-five percent of the patients who did not achieve a CR but survived their first salvage attempt received a second salvage attempt, which produced a CR in 2%. CR rates with first salvage therapy were higher in patients given the known active regimens than in patients given the investigational single agents, eg, 16 of 25 versus ½ in patients with first CRs exceeding 2 years, 20 of 43 versus 2 of 13 ($P = .04$) in patients with first CRs of 1 to 2 years and 21 of 181 versus 1 of 62 ($P = .02$) in patients with shorter first CRs or with primary refractory AML. We compared survival in patients who went into CR (n = 61) with survival in patients who did not but lived at least 10 weeks after start of first salvage (n = 188), by which time 97% of the patients who ultimately achieved CR were in CR. Only 3 of the patients in CR died before week 10. The log-rank *P* value for the comparison was <.001, suggesting a survival advantage from CR. This advantage was seen both in patients with first CR durations of 0 to 12 and 12 to 24 months, at least as judged by the Gehan test. This test is more robust for earlier parts of the survival curve than the log-rank test.[4] Indeed, the difference between the CR and no CR groups is almost exclusively in the first 2 years. This can be seen in Table 1. The probability of survival at 24 months even among patients achieving a second CR after an initial CR of 0 to 24 months is <.2 (Table 1). However, patients achieving a second CR after an initial CR of 12 to 24 months had a .73 ± .10 probability of survival at 12 months versus a .27 ± .1 probability for similar patients whose disease failed to respond to first salvage therapy, whereas survival expectations were very similar for patients with first CR durations less than 1 year or who were primary refractory regardless of whether they achieved a CR with first salvage therapy (Table 1). Forty-one of the 48 patients who died after obtaining a CR with first salvage therapy had a recurrence before death. The other 7 died in CR. Actuarial median second remission duration was approximately 12, 28, and 30 weeks for patients with first CR durations of less than 12, 12 to 24, and greater than 24 months, respectively. Including only the 57 of the 61 second CR patients who received known active agents does not materially affect the results presented above.

Our results suggest that achieving a CR confers a survival benefit to patients with AML receiving first salvage therapy, although the data only permit analysis in patients with initial CR durations less than 2 years (Table 1). Furthermore, our data suggest that investigational single agents usually produce lower CR rates than accepted therapies such as HDAC. However, whether patients with AML recurrent after initial CR durations less than 2 years should always receive accepted therapies for first salvage depends on the value the reader places on the survival probabilities for CR patients shown in Table 1. In our opinion, provided that an allogeneic transplant is not an option, administration of investigational single agents is justified in patients with initial CR durations of 1 to 2 years and is indicated in patients with shorter first CRs including, of course, patients with primary refractory disease.

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The 20210A Allele of the Prothrombin Gene Is an Independent Risk Factor for Perception Deafness in Patients With Venous Thromboembolic Antecedents

To the Editor:

One of the main factors of sudden hearing impairment, vestibular disturbance, or tinnitus is generally thought to be an acute labyrinthine ischemia of varying degrees. Despite the most common mechanism of sudden hearing loss appearing to be impaired cochlear blood circulation,[1] the scientific basis of this assumption has not yet been proven. Experimental studies performed in animals through ferromagnetic obstruction of cochlear blood vessels have shown that vascular impairment of the inner ear results in a considerable decrease in intracochlear oxygenation, causing a significant loss in the auditory response.[2] In humans, deafness associated with small infarctions of cochlear tissue

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have exceptionally been reported in the context of rare multifocal microangiopathic encephalopathies,[3] but no data are available in the field of current sudden hearing impairment.

Our attention was stimulated by some of our patients with thromboembolic disease who spontaneously reported unilateral acute perception deafness. We thus performed a retrospective case-control study.

Three hundred sixty-eight patients, corresponding to 101 men and 267 women, median age 41 years (range, 17 to 72), with antecedents of spontaneous deep vein thrombosis (thrombosis group: TG), were investigated over a 3-year period in the outpatient Department of Hematology. Eighteen of them, 12 women and 6 men, 38 to 69 years old, had also suffered from acute unilateral hearing impairment. Explorations were in favor of a pure unexplained perception auditory defect, with computed tomography scanning and magnetic resonance imaging showing no cerebral lesion. These 18 patients had no antecedents of symptomatic atherosclerosis, except the oldest man who had angina pectoris, and ultrasound exams performed on asymptomatic patients gave no evidence of atherosclerotic lesions on carotid arteries. None of the women had hypertension and seven of them were smokers: the three youngest, aged 38, 43, and 45 years, were also oral-contraceptive takers. Three of the men were heavy smokers, including the one with angina pectoris; two of them had mild hypertension.

During the same period of time, acute unilateral perception deafness could only be found in 4 of 395 nonthrombotic consecutive patients studied for hemorrhagic symptoms or thrombocytopenia (hemorrhage group: HG), and in 6 of the 395 nonthrombotic and nonhemorrhagic sex- and age-matched control individuals (control group: CG) who had a systematic medical check-up in a Public Health Center (Pearson chi-square test: $P = .0008$). No difference could be evidenced between the hemorrhage group and the control group.

Concerning biological risk factors for thrombosis, the prothrombin 20210A allele was positive in 25 patients from TG (6.8%), in 4 patients from HG (1%), and in 3 patients from CG (0.7%) ($P = .0008$). The factor V gene G1691A mutation (factor V Leiden) was positive in 63 patients from TG (61 heterozygous and 2 homozygous; 17.1%), in 5 from HG (1.3%), and in 6 from CG (1.5%; $P < .0001$). Antithrombin deficiency was evidenced in 5 patients from TG (1.4%), but in none from HG or CG ($P = .005$). Protein C deficiency was found in 11 patients from TG (3%), in 2 patients from HG (0.5%), and in 3 patients from CG (0.8%; $P = .006$). Protein S deficiency was confirmed in 8 patients from TG (2.2%), in 1 patient from HG (0.25%), and in 1 patient from CG ($P = .005$). Antiphospholipid antibodies could be found in 35 patients from TG (9.5%), in 6 patients from HG (1.5%), and in 7 patients from CG (1.8%; $P < .0001$). Concerning the type of positive antiphopholipid antibodies, a lupus anticoagulant was found in 22 patients from TG but in only 4 patients from HG and 5 patients from CG ($P < .001$). Twenty-seven patients from TG had positive anticardiolipin IgG antibodies whereas only 3 patients from HG and 4 patients from CG were positive ($P < .001$). Finally, 23 patients from TG were positive for anti–β2-glycoprotein I IgG antibodies, but only 3 patients from HG and 2 from CG ($P < .0001$). The prevalence of positive biological risk factors for thrombosis was the same in the hemorrhage group and in the control group.

Due to the absence of differences in terms of prevalence of deafness and of biological risk factors for thrombosis, we defined a normal group as the addition of the hemorrhage group and of the control group. Taking into account this reference group and the thrombosis group, we calculated crude odds ratios (cOR) for perception deafness and 95% confidence intervals ($_{95\%}$CI) using logistic regression for each biological venous thrombosis risk factor and for thromboembolic antecedents (Table 1). Thereafter, a multivariate logistic regression was performed to adjust to potential confounding factors (adjusted odds ratio, aOR; a stepwise procedure entering each variable with P lower than .20 in monovariate logistic regression; table 1): only a positive thromboembolic antecedent and a positive prothrombin gene 20210 A allele were confirmed to be independent risk factors for perception deafness.

Among the 18 thrombotic patients with deafness, 6 were heterozygous carriers of the prothrombin gene 20210A allele. Among these 6 carriers were the 3 young smoking and oral-contraceptive–taking women, another nonsmoking woman and two smoking men, including the oldest one with angina pectoris. The introduction of gender, oral contraceptives, and smoking as new parameters for logistic regression analysis gave nonsignificant results, showing that these parameters are not independent risk factors for perception deafness: results concerning smoking are concordant with available published data.[4] However, in young thrombotic women with the 20210A allele in the prothrombin gene, we cannot exclude that smoking and oral contraceptive use may be clinical cofactors of the disease.

In conclusion, these data seem to indicate that, in patients with thromboembolic antecedents, the prothrombin 20210A allele is an independent risk factor for perception deafness. This may constitute a new indirect argument for the vascular/thrombotic origin of some of these accidents. As a consequence, patients with thrombotic antecedents and the prothrombin 20210A allele should be preserved from aggressive conditions for the internal ear (excessive noise, scuba diving, treatments with a known specific toxicity, etc). If patients are young women, as they may be putative clinical cofactors, hearing preservation may be an additional argument for oral contraceptive and smoking cessation. The prothrombin 20210 allele has already been described to increase the risk of myocardial infarction among non-Mediterranean young women and the relative risk was higher in smoking carriers.[5] We have previously described cases of spinal cord infarction in young smoking and oral-contraceptive–taking women with the prothrombin 20210A allele.[6] The 20210A allele of the prothrombin gene may thus have a more general status of risk factor for arteriolar thrombosis, a generally difficult-to-diagnose and sometimes silent event. Some anatomical localizations, due to their

Table 1. Odds Ratios and $_{95\%}$CI for Perception Deafness and Type of Positive Biological Risk Factor for Thrombosis in Thrombotic Patients, With the Normal Group as Reference: Results of the Univariate and of the Multivariate Logistic Regressions

	Monovariate Logistic Regression			Multivariate Logistic Regression Model		
	cOR	$_{95\%}$CI	*P*	aOR	$_{95\%}$CI	*P*
Thromboembolic antecedents	4.0	1.8-8.8	.0005	2.4	1.1-5.9	.049
Prothrombin gene 20210A allele	13.7	5.1-37	$<10^{-4}$	9.3	3.2-27	$<10^{-4}$
Factor V gene G1691A mutation	3.3	1.2-9	.02	1.8	0.6-5.6	.31 NS
Antithrombin deficiency	10^{-4}	0-10^{250}	.98 NS	/	/	/
Protein C deficiency	10^{-5}	0-10^{250}	.98 NS	/	/	/
Protein S deficiency	4.6	0.6-38	.15 NS	3.5	0.4-30	.26 NS
Positive antiphopholipid Ab	4.1	1.4-12	.01	10^{-11}	0-10^{250}	.98 NS
Positive lupus anticoagulant	3.1	0.7-14	.13 NS	0.2	0.02-3.1	.27 NS
Positive anticardiolipin IgG Ab	6.1	2.0-19	.0015	10^{6}	0-10^{250}	.98 NS
Positive anti–β2-glycoprotein I IgG Ab	7.4	2.4-23	.0005	1.5 10^{6}	0-10^{250}	.98 NS

In the multivariate model, odds ratios for each variable are adjusted for the 7 other variables.
Abbreviations: Ab, antibodies; NS, nonsignificant.

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dramatic consequences, are however evident. Future questions should address the identification of the spectrum of additional abnormalities acting to increase the penetrance of clinical arteriolar thrombotic manifestations associated with the prothrombin 20210A allele.

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Where Does Platelet Factor V Originate?

To the Editor:

I have read with interest the article by Camire et al[1] proposing ''endocytosis by megakaryocytes as the major mechanism by which platelet-derived factor V is acquired. . . .''

The approach is clever, identifying the type of factor V derived from two patients, each heterozygous for factor V Leiden, who received allogeneic transplantation of bone marrow and liver, respectively, from a donor with wild-type factor V.

The only data presented in detail is a series of four Western blots and, while the patterns exhibited are consistent with the hypothesis, this technique does not lend itself well to quantitative evaluation. In fact, the conclusion is based in part on the failure to demonstrate platelet uptake of factor V, an experiment presented within the text and as ''data not shown.'' Moreover, the authors did not attempt to show that megakaryocytes can endocytose factor V. Further, the possibility that the result of the transplant is a chimera is not considered in detail.

Against this proposition are two reports from my laboratory indicating that factor V can be biosynthesized in guinea pig platelets[2] and in human megakaryocytes[3] performed by the incorporation of radiolabeled amino acids into factor V. A third report from our group, in collaboration with Alan Gewirtz, indicates that mature human megakaryocytes bind and synthesize factor V and have mRNA for factor V.[4] Thus, the question is not whether there is biosynthesis, but whether uptake or synthesis is the ''major'' mechanism.

In a recent study from the laboratory of Ginsburg[5] using factor V ''knockout'' mice transplanted with marrow progenitor cells, different cellular origins for the biosynthesis of murine plasma factor V and murine platelet factor V were demonstrated, suggesting that free interchange does not take place in a situation in which greater than 80% engraftment occurs. Because the differences between mice, guinea pigs, and humans could be caused by true biological variability, this study supports, but does not prove, that platelet factor V derives from megakaryocytes. Nevertheless, Camire et al have not excluded an important contribution to platelet factor V from megakaryocyte biosynthesis because they have not adequately addressed the effect of bone marrow chimerism on their results, and have perhaps overestimated the ability of Western blotting to quantify the concentration of factor V.

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