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Protein Z plasma levels are not associated with the risk of coronary heart disease: the PRIME Study

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Protein Z, a vitamin K-dependent plasma glycoprotein, is thought to play a role in coagulation by serving as a cofactor to increase the inhibition of factor (F)Xa by a protein Z-dependent protease inhibitor by more than 1000 times [1,2]. Both *in vitro* and mice studies led to speculation that protein Z deficiency could be a risk factor for thrombosis in humans [1,3]. However, epidemiological data on the role of protein Z are based on retrospective studies and provide conflicting results [4–10]. We aimed to determine whether plasma levels of protein Z could influence the risk of coronary disease using the Prospective Epidemiological Study of Myocardial Infarction (PRIME) prospective cohort. The design of this nested case-control study was extensively reported elsewhere [11,12]. The PRIME Study was initially designed to explain the several-fold differences in risk of coronary heart disease between France and Northern Ireland. Briefly, over 10 000 apparently healthy men recruited in France (Lille, Strasbourg, Toulouse) and Northern Ireland (Belfast) were included in the study. The risk of future coronary events was almost two times higher in Northern Ireland than in France, this difference being not adequately explained by conventional cardiovascular risk factors [11,12]. We measured baseline plasma concentration of protein Z antigen among 297 participants who subsequently developed coronary events and in 593 age-matched controls who remained free of disease over the 5 years of follow-up. Determination of protein Z was

performed with a commercially available ELISA (Asserachrom Protein Z Diagnostica Stago, Asnières, France), following the manufacturer's instruction. The interassay coefficient of variation was 7.1%.

Plasma protein Z was not associated with any of the conventional cardiovascular risk factors [hypertension, smoking status, diabetes, body mass index, total cholesterol, high-density lipoprotein cholesterol and C-reactive protein (CRP), data not shown]. Baseline concentrations of protein Z were not significantly different between individuals who experienced a coronary event during follow-up and those who did not, either in the whole cohort or when considering each country separately (Table 1). Protein Z concentrations were similar among individuals with myocardial infarction or coronary death and those with angina pectoris (mean $\pm$ SEM: 1.56 ± 0.05 vs. 1.61 ± 0.05 mg L⁻¹, respectively; $P = 0.29$). Plasma protein Z levels were higher in Northern Ireland than in

Table 1 Means (SEM) of plasma protein Z in cases and controls and relative risk of coronary event associated with 1 SD increase of protein Z level

	Controls (France/ N. Ireland; $n = 344/249$)	Cases (France/ N. Ireland; $n = 172/125$)	P^*	Relative risk (95% confidence interval)
All†	1.64 (0.03)	1.58 (0.04)	0.17	0.90 [0.78–1.05]
France	1.58 (0.03)	1.57 (0.05)	0.65	0.95 [0.78–1.17]
Northern Ireland	1.72 (0.04)	1.61 (0.06)	0.13	0.84 [0.64–1.05]
P^{**}	0.01	0.47		

Values are in mg L⁻¹. * P for difference between cases and controls are derived from conditional logistic regression. ** P for difference between France and Northern Ireland. †Means and relative risk are adjusted for population.

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France (mean $\pm$ SEM: 1.68 ± 0.03 vs. 1.58 ± 0.03 mg L⁻¹; $P = 0.01$). This difference appeared stronger in controls than in cases (Table 1), even though the interaction did not reach significance ($P = 0.38$).

As two studies have suggested a threshold effect in which low levels of protein Z increased the risk of thrombosis [4,6], we have stratified the population into two groups according to the 10th percentile of the distribution in controls. In the whole cohort, 10 percent ($n = 58$) of healthy controls had protein Z levels below 0.93 mg L⁻¹ (10th percentile = 0.93 mg L⁻¹). Eleven percent ($n = 32$) of the patients had protein Z levels below this cut-off ($P = 0.58$), which means that protein Z below 0.93 mg L⁻¹ was not a risk factor for coronary disease. This was homogeneous across countries as 12% ($n = 21$) and 10% ($n = 12$) of the patients, in France and Northern Ireland, respectively, had protein Z levels below the 10th percentile which was set in controls for each country separately ($P = 0.47$ and 0.80 for case-control difference in France and Northern Ireland, respectively).

In conclusion, antigenic protein Z levels do not seem to have a major effect on the risk of coronary heart disease in healthy men followed for 5 years.

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Aspirin resistance *in vitro* and hypertension in stroke patients

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Aspirin reduces the relative risk for cerebral events in patients with cardiovascular or cerebrovascular disorders by approximately 23% [1]. Despite its large use, there are concerns about

the efficacy of aspirin and methods to evaluate it [2,3]. Indeed, it appears that the antiplatelet effect of aspirin is not uniform in all patients and previous studies estimated that 8–45% of the population were aspirin resistant [4–8]. Most studies have focused on patients with coronary artery disease, although a few reports have identified aspirin resistance in patients with stroke or cerebrovascular disease [6–9]. In this study we evaluated aspirin resistance *in vitro* using the PFA-100® method, in 37 patients (20 women and 17 male; mean age = 60 ± 14.7 years) treated with aspirin 160 mg d⁻¹ for secondary prevention of stroke (28 cerebral infarcts, nine transient

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