increase from north to south, has been described in the European population. Thus, the inconclusiveness of the results of some previous studies may be due to geographic factors, since they included subjects from populations with a low prevalence of the protective alleles. Also, the predictive power of individual polymorphisms may vary among populations according to differences in the overall prevalence of risk factors and differences in gene–environment interactions.

Among the patients with coronary artery disease in our study, the mean levels of factor VIIa did not differ significantly between those with a history of myocardial infarction and those without it, despite the different distributions of genotypes in these two groups. Several factors may account for this finding. First, homozygotes for the protective alleles were a minority in each group. Second, whereas genotype analysis was performed for all the patients, data on factor VIIa levels from a substantial number of patients could not be included because these patients were receiving concomitant anticoagulant therapy. Moreover, it is well accepted that precise genetic markers may provide a better measure of individual lifelong exposure to a putative risk factor than related plasma measurements, which may vary over time. This may be particularly true of factor VIIa levels. Whereas genetic markers are probably the strongest determinants of these levels, a number of well-known, transient, environmental influences may obscure the relation with myocardial infarction when a single measurement is made.

In addition, it is important to recognize that none of the polymorphisms we investigated have been definitively proved to be functional. Expression studies have indicated that the R353Q polymorphism may modulate the secretion of factor VII. Others have shown that the polymorphism involving the A1 and A2 alleles, in the promoter, may reduce the rate of transcription, with ensuing reductions in the synthesis of factor VII. Indeed, there is linkage disequilibrium between the two polymorphisms, with a degree of allelic association of more than 80 percent, as confirmed in the current study. Recently, van 't Hooft et al. described the functional effect of another polymorphism in the factor VII promoter (a substitution of thymine for guanine at position -401), which exhibited complete association with the polymorphism involving A1 and A2. This polymorphism at position -401 strongly influenced the binding of nuclear proteins and was associated with a reduced rate of transcription. The slightly stronger relation we found for the 5′F7 polymorphism as compared with the R353Q polymorphism may be in accordance with this finding.

A limitation of our study is the case–control design; the results need to be confirmed in prospective cohort studies. The Thrombosis Prevention Trial recently showed that low-dose regimens of oral anti-coagulants independently reduce the rate of death due to coronary heart disease in men at high risk for cardiovascular events. Remarkably, the low-normal factor VII levels resulting from low-dose warfarin treatment substantially overlap those associated with the protective factor VII genotypes. Such a pharmacologic approach could be effectively restricted to persons with “unfavorable” genotypes; those with the protective genotypes could be excluded because of the low probability of benefit and increased risk of bleeding.

In conclusion, our results add evidence of the role of factor VII genotypes in modulating the risk of myocardial infarction. In particular, they may help explain why some patients are at low risk for myocardial infarction, despite the presence of severe, angiographically documented coronary artery disease. In the future, genotyping for factor VII genetic markers may help identify subgroups of patients with coronary artery disease who might benefit from various therapies.

Supported by grants from the Veneto Region, the Cariverona Foundation, and the Ministero dell’ Università e della Ricerca Scientifica e Tecnologica (to Ds. Cornofero and Girelli) and from Telethon project E.675 and the National Research Council target project on Biotechnology (to Professor Bernardi).

We are indebted to Mr. Diego Minguzzi for excellent technical assistance, to Mrs. Mirella Chesi for assistance in collecting data, and to Dr. Marco Sandri, Center for Scientific Calculation, University of Verona, for helpful suggestions.

REFERENCES