Editorial comment
Anti-heparin antibodies: are they innocent in the long run?

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The study by Mattioli et al.[1], published in this issue of the journal, suggests that anti-heparin antibodies may worsen the thrombosis free survival of unstable angina patients treated with unfractionated heparin. This hypothesis is based on a higher incidence of thromboses in positive antibody patients compared to patients with intermediate or negative test. The fact that anti-heparin antibodies may be associated with increased thrombotic risk is a novel observation which may further complicate the apparently paradoxical link between heparin treatment and thromboses. The occurrence of thrombotic events during heparin administration was first observed over 40 years ago[2]. More recently, thromboses have been recognized as being part of a relatively frequent adverse reaction known as heparin-induced thrombocytopenia (HIT)[3]. A drop in the platelet count during heparin administration occurs quite commonly and causes marked thrombocytopenia in 3 to 15% of treated subjects[4]. Two different HIT types have been identified. The HIT type 1 is usually mild and transient. It has been observed within the first few hours of the start of the heparin treatment, it is not immunologically mediated, has no association with thrombotic complications, and does not require heparin withdrawal. The more severe HIT form (type 2) is observed after at least 5 days of treatment and can be associated with devastating thromboses. No specific treatment is available, early HIT recognition being the only effective prevention. Thus, monitoring the platelet count during heparin treatment has become mandatory. Both thrombocytopenia and thromboses associated with type 2 HIT are caused by the development of antibodies which induce platelet aggregation and release. Essential clues to the understanding of mechanism(s) linking antibody production and coagulative system activation were provided by the demonstration that the antibody target is constituted by a complex formed by heparin with platelet factor 4 (PF4). This is a heparin binding protein contained in platelet α-granules and readily released after platelet activation. The immune complexes formed at certain antibody:heparin:PF4 ratios are bound by platelets through their Fc platelet receptor and this binding is able to initiate platelet activation. Endothelial cells also participate in this process[5] and may play a role in the pathogenesis of HIT. The elucidation of the HIT antibody target has significantly improved our laboratory tools for antibody recognition. Using ELISA methods anti-heparin-PF4 complex antibodies have been shown to be surprisingly common. As many as 60% of patients treated with unfractionated heparin develop antibodies[6]. Why do only a minority of them show a significant drop in the platelet count? The possibility that some thrombocytopenias are masked by the reactive thrombocytosis occurring in many clinical conditions requiring heparin therapy should be certainly considered. But why are clinical manifestations of antibodies so different? If antibody titer is an important variable, should we avoid re-exposure to heparin in all subjects developing antibodies? Ge-

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netic factors also play a role. In patients with HIT, in fact, the his_{131} is more common than the arg_{131} FcγIIa phenotype[7]. This has been explained by the fact that the two Fc receptor isoforms are differently sensitive to IgG1, which is the predominant Ig subclass of HIT antibodies[8]. Elucidating the various determinants which influence HIT manifestations may help to identify subjects at higher risk. Some other unresolved questions will, however, remain. An important issue is related to the safety of low molecular weight heparins. The risk of HIT with these molecules is reduced but not absent. How frequent is the development of antibodies in patients treated with low molecular weight heparins? Another general question is the biological and clinical significance of the antibodies in the absence of thrombocytopenia. The so-called serological HIT is very common and the possibility that platelet and endothelial cell activation may be increased in these patients should not be overlooked. These mechanisms may lead to an increased thrombotic risk thus making the hypothesis raised by Mattioli et al.[1] biologically plausible. However, the hypothesis is based on a very limited size study. Positive antibody patients were few and quite unbalanced for major risk factors. The need for large size clinical studies in this field is obvious and the preliminary observation published in this issue constitutes a further stimulus to perform such studies.

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