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The role of new antithrombotics

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Following the landmark study by Barritt and Jordan in 1960, who randomized patients with venous thromboembolism to no treatment or a combination of heparin and warfarin, antithrombotic therapy for this disease became widely accepted. Their study had to be stopped prematurely because half of the non treated patients had recurrent pulmonary embolism or died of it. Subsequent studies revealed that an initial course of heparin is really necessary. Omitting heparin and only giving Vitamin K antagonists resulted in a 3 to 4 fold increase in the incidence of venous thromboembolism during the months following the initial event. It was also well documented that heparin was most safely administered by continuous intravenous infusion and that adequate plasma concentrations in the first 48 hours were crucial in order to reduce the risk of later recurrences. Finally, two randomized studies indicated that a course of 5 days of heparin was comparable to 10 days in terms of efficacy. Hence, since the 1990's the standard therapy for venous thromboembolism consisted of an initial 5-7 day course of intravenous heparin, carefully titrated by the activated partial thromboplastin time, with an immediate start of warfarin, which was to be continued for at least 3 months. In the early 1990's the first clinical studies with low molecular weight heparins were performed. These products are derived from the original heparin and have several advantages over the parent compound. These include a longer half life, almost complete bio-availability and simple one or twice daily subcutaneous administration without the need for laboratory monitoring. Thusfar, at least 13 well designed randomized studies have compared intravenous, dose-adjusted heparin with subcutaneous,

non-monitored low molecular weight heparin for the initial treatment of patients with established symptomatic venous thromboembolism. Meta-analyses have clearly revealed that the treatment with low molecular weight heparin is superior both in terms of efficacy (i.e. recurrence of thrombosis) and safety (i.e. major bleeding). The recurrence rate in the first three months is reduced by approx 40%, whereas the incidence of major hemorrhages is almost halved. Therefore, at present low molecular weight heparin have replaced heparin in the treatment of venous thromboembolism. The development of the pentasaccharide is another option to further improve the outcome in these patients. Parallel studies, in patients with deep vein thrombosis or pulmonary embolism have been completed recently, and revealed a comparable efficacy and safety of these short acting pentasaccharides relative to unfractionated heparin and low molecular weight heparin for the initial treatment. Furthermore, a slightly modified pentasaccharide, which provides antithrombotic protection for one week after subcutaneous injection has become available for clinical evaluation in patients with venous thromboembolism and initial clinical experience is favourable in comparison to the combination of heparin and vitamin K antagonist. Finally, several orally active small molecules have become available for the treatment of venous thrombotic disease. Ximelagatran, an oral thrombin inhibitor, has successfully been studied both for the acute and longterm treatment. The evidence from clinical studies with these novel agents will be reviewed with a special emphasis on the treatment of venous thromboembolism in cancer patients.