VENA CAVA FILTERS

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The appropriate use of caval vein filters in patients at risk for PE or to prevent recurrent PE controversial. While, the attractiveness of filters is appealing due the lack of bleeding complications, as with anticoagulant treatment, once inserted, and their physical protection for clots that are destined for the pulmonary circulation, their use is not based on sound evidence. There are multiple reports of case series of patients who were treated with caval vein filters that show minimal rates of complications. However, the single large randomized trial showed that an initial benefit (reduction of pulmonary embolism) was lost due to an excess of recurrent deep vein thrombosis later on, with no difference in mortality.

However, the appraisal of the data is challenging, since new developments on technology of caval vein filters are rapid, both in insertion techniques, retrieval techniwues for temporary filters, and minimization of coagulant potential of the filters surface. Hence, future clinical trials with these devices in patients at a high riskof (fatal) recurrent pulmonary embolism seem worthwhile.

Currently, it seems best to reserve the use of caval vein filters for the rare cases of patients with venous thromboembolism who cannot be treated with anticoagulants. It is likely that in case of a reversible condition that prohibits current use of anticoagulants the use of a truly retrievable filter is the treatment of choice. Another, situation where the application of a caval filter seems appropriate is the situation where recurrent disease occurred during adequate treatment with anticoagulants as a third line option (first line: vitamin K antagonists; second line: long term low molecular weight heparin).

In conclusion, routine use of caval vein filters is not appropriate; they may be used in rare clinical situations where anticoagulant treatment is impossible, or adequate anticoagulant treatment failed.

PROPHYLAXIS AND TREATMENT OF THROMBOEMBOLISM

THE FIRST AMBULATORY SCREENING ON THROMBOEMBOLISM (FAST): A MULTICENTRE, CROSS-SECTIONAL, OBSERVATIONAL STUDY ON RISK FACTORS FOR VENOUS THROMBOEMBOLISM

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Summary. Objectives: to assess the prevalence of risk factors for venous thromboembolism and the prevalence of recent (<1 year) venous thromboembolism (VTE) (including superficial vein thrombosis, deep vein thrombosis and pulmonary embolism) amongst patients attending general practitioner surgeries. Design: multicentre, cross-sectional, observational study. Setting: 1,536 general practitioner surgeries. Participants: 15,180 adult, co-operative subjects, who had consulted their general practitioner for a health disorder and signed the informed consent form.

Interventions. None

Main outcome measures. Prevalence of known VTE risk factors graded according to importance, and prevalence of recent (<1 year) VTE events (including superficial vein thrombosis), based on interviews.

Results. About 1:5 patients had at least one strong risk factor and about 1:20 had at least two risk factors, with no difference between sexes. The prevalence of strong risk factors increased with age. Most were related to medical conditions: history of superficial venous thrombosis and/or deep vein thrombosis /pulmonary embolism, heart failure and malignancy. About 3:4 women and 2:3 men had at least one moderate to weak risk factor; nearly 1:2 women and 1:3 men had at least two moderate to weak risk factors. The most common were: history of VTE, smoking, history of miscarriage, oestrogen therapy, obesity and varicose veins. Overall, 80% women and 67% men had at least one risk factor, and 50% women and 35% men had at least two risk factors.

The prevalence of recent (<1 year) VTE was 3.4% in women and 2.4% in men, and increased with age. The majority of cases were superficial venous thrombosis in both sexes (2.5% in women and 1.5% in men).

Conclusions. The prevalence of risk factors for VTE amongst patients attending general practitioner surgeries is high. General practitioners should bear this in mind during their daily practice.

THE OPTIMAL DURATION OF ORAL ANTICOAGULANT THERAPY IN PATIENTS WITH VENOUS THROMBOEMBOLISM

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It has been clearly demonstrated that patients with acute venous thromboembolism (VTE) who are treated with full doses of unfractionated or low-molecular-weight heparin have a very high rate of recurrence unless effective antico-

agulant therapy is continued after the initial treatment. The observed difference in recurrence rates between patients with and without reversible risk factors is relevant to the issue of optimal duration of oral anticoagulant therapy. The long-term prognosis of patients in whom VTE occurs following exposure to temporary risk factors is excellent. Accordingly, they do not require further anticoagulation following the initial three-month period. Patients with continuous risk factors and those with idiopathic thrombosis have a two to three-fold increased risk of recurrence as compared with patients who developed a thrombotic event in association with a transient risk factor. Several randomized clinical trials have clearly demonstrated that long-term anticoagulant therapy is effective in preventing recurrences in these patients, but carries a risk of bleeding and is inconvenient. Accordingly, the optimal duration of oral anticoagulant therapy is still controversial. Recent studies suggest that low-intensity warfarin therapy, after an initial three to six-month period of conventional anticoagulation, may confer an additional protection without an excessive bleeding risk. New categories of drugs are emerging, such as pentasaccharides and thrombin-inhibitors, which have the potential to simplify the long-term treatment of patients with VTE by obviating the need for periodic laboratory monitoring, and seem associated with a more favourable benefit-to-risk ratio. Furthermore, recent studies suggest that the risk for late recurrences can be carefully predicted on individual basis by strategies that include the ultrasound assessment of thrombotic burden or the laboratory evaluation of D-dimer.

RESIDUAL VENOUS OBSTRUCTION AND D-DIMER AS PREDICTORS OF RECURRENT VENOUS THROMBOEMBOLISM

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The optimal duration of secondary prophylaxis with oral anticoagulants after a first episode of venous thromboembolism (VTE) is controversial. Approximately one-third of patients with apparently unprovoked VTE will experience a new thrombotic episode over the subsequent decade once anticoagulant therapy is stopped, regardless the duration of secondary prevention. In recent years, several studies have investigated risk factors associated with the risk of VTE recurrence to optimise secondary prophylactic strategies. Among others, elevated D-dimer levels and residual venous obstruction (RVO) have been related to an increased risk of recurrence. Plasma D-dimer levels have been shown to decrease during therapy with vitamin K antagonists and to increase in some patients after oral anticoagulation withdrawal. A number of studies were specifically developed to test as a primary end-point the prognostic accuracy of D-dimer measurement after anticoagulation withdrawal in predicting VTE recurrence. In all studies, patients with recurrence had significantly higher D-dimer levels compared with those without. The results of a recently completed randomized clinical trial supported these findings by showing a statistically significant reduction in the rate of VTE recurrence in patients with elevated D-dimer levels randomized to resume oral anticoagulant therapy as compared to patients randomized to treatment withdrawal. The results of recent trials also suggested that RVO may predict recurrent VTE. RVO is more common in patients with multiple episodes of VTE or in patients with permanent risk factors for VTE than it is in patients with a single episode of VTE and/or transient risk factors, and is clearly associated with a significantly increased risk of recurrent VTE. Management studies based on RVO have been recently completed or are still undergoing.

PROPHYLAXIS OF VENOUS THROMBOEMBOLISM IN ORTHOPEDIC SURGERY

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Current anticoagulant provision is dominated by parenteral heparins and oral warfarin that act by inhibiting several steps of the coagulation pathway indirectly. There is an unmet need for oral anticoagulants that offer efficacious, but primarily safe, unmonitored anticoagulation. During the past 10 years, research efforts have been increasing to identify small molecule inhibitors of the coagulation enzymes as novel therapies for thrombotic disorders. In the past year, there has been particular success in developing non-peptidic, orally available, small molecules to directly inhibit the key proteases, Factor IIa and Factor Xa. The clinical development of these new anticoagulants is following the well-tested strategy of dose ranging and registration studies in major orthopaedic surgery, prior to development in arterial indications. Of the new oral anticoagulants in development, the two agents in the most advanced stage are dabigatran etexilate and rivaroxaban, which inhibit Factor IIa and Factor Xa, respectively. Other agents in the early stages of development include several Xa inhibitors and a Factor IXa inhibitor. It is anticipated that over the next three years, at least one of these agents will be successfully licensed for the prevention of venous thromboembolism after major orthopaedic surgery, which will act as a facilitator for the gradual replacement of the current anticoagulants with new, oral, safe and unmonitored drugs.

NEW ANTICOAGULANT DRUGS IN VENOUS AND ARTERIAL THROMBOSIS

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New anticoagulants that do not require coagulation monitoring, and are preferably oral, are urgently required as alternatives to heparin, low molecular weight heparins and the vitamin K antagonists. A large number of targets involved in clotting, including regulatory enzymes and serine protease mediators, are under investigation. Treatment of various thromboembolic disorders with recombinant forms of naturally occurring proteins, such as tissue factor pathway inhibitor (tifacogin), activated protein C (drotrecogin α) and soluble thrombomodulin (ART-123), has been investigated, with varying degrees of success. Fondaparinux, a subcutaneous, indirect Factor Xa inhibitor, is approved for the prevention and treatment of venous thromboembolism (VTE) in certain indications, and showed positive results in patients with acute coronary syndromes. Idraparinux, a subcutaneous, long-acting, indirect Factor Xa inhibitor, is still in development. Direct inhibition of thrombin or Factor Xa with synthetic, small molecules is an attractive strategy for the development of novel anticoagulants. After the withdrawal of ximelagatran, dabigatran is now the furthest-advanced oral, direct thrombin inhibitor, and an extensive phase III clinical trial programme (the RE-VOLUTION trials) has recently started, to determine its efficacy and safety in several key indications. Direct Factor Xa inhibitors in development which show clinical promise in various indications include rivaroxaban (BAY 59-7939), LY517717, YM150, and DX-9065a and its oral formulation DU-176b. Rivaroxaban is the furthest-advanced oral, direct Factor Xa inhibitor in development. It had a favourable efficacy and safety profile, relative to enoxaparin, in phase II trials in the prevention of VTE after major orthopaedic surgery - phase III trials (the

RECORD trials) were initiated in late 2005. The results of phase II trials of rivaroxaban for the treatment of proximal deep vein thrombosis are also expected soon. With so many compounds in development, alternatives to the established anticoagulants may be available soon.

AREAS OF CERTAINTY – AND UNCERTAINTY – ABOUT BEST DOSAGES OF NEW ANTICOAGULANTS

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Recommended dosages of new anticoagulants to be administered to patients arise from clinical trials and should represent best estimates, with awareness that subsequent patients may differ in response. Nonetheless, decisions must be taken in selecting the dosages to be used in early human studies. One decision relates to balancing the twin goals of maximizing knowledge and minimizing risk to human subjects. Another related decision particularly relevant for anticoagulants relates to whether risk tolerance (e.g., for bleeding and efficacy) may differ depending on the indication, e.g., primary prophylaxis vs treatment of established thrombosis. A third decision relates to how subject risk is balanced against desired speed of drug development. There are other related decisions, including sample size, which can help make estimates of risk (for efficacy failure or adverse events) more or less robust, affecting future risk to other study subjects. Sample size choices can be driven by hypotheses that allow faster study completion but with riskier dosages.

These decisions are best informed by maximizing, within reason, the quality and quantity of data preliminary to each step. Relatively inexpensive studies performed with past anticoagulants include those in living animal models, tissue explants, *in vitro* systems, and ex vivo samples from human volunteers. Examples of these will be presented. Past published examples of choices in anticoagulant development will also be presented. Final suggested principles will be presented for consideration by the audience. They include: (1) The tolerance for treatment failure in primary prophylaxis, assessed by venography, can be higher than the tolerance for treatment failure of established thrombosis, (2) Finding the *minimum effective dose* is not an appropriate goal for treatment of a life-threatening condition if available therapy is highly effective, and (3) Monitoring for possible surrogate markers of efficacy and safety is desirable in clinical trials, whether or not their monitoring is planned to be a part of eventual usual treatment.

MECHANISMS IN HEMOSTASIS AND THROMBOSIS - II

THE INTERACTIONS BETWEEN INFLAMMATION AND COAGULATION

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Recent studies have emphasized the important contribution played by inflammation in stimulation of the coagulant responses. Inflammatory mediators initiate coagulation, decrease the activity of natural anticoagulant mechanisms and impair the fibrinolytic system. The natural anticoagulants function to dampen elevation of cytokine levels. Components of the natural anticoagulant cascades, like thrombomodulin, can minimize endothelial cell dysfunction by rendering the cells less responsive to inflammatory mediators, facilitate the neutralization of some inflammatory mediators and decrease loss of endothelial barrier function. Thus, decreased anticoagulant pathway function not only promotes thrombosis but also amplifies the inflammatory process. The magnitude of the down regulation of the specific anticoagulant mechanisms varies markedly from vascular beds, possibly contributing to the reasons that some organs are more prone to injury in inflammatory diseases than others. Once the inflammation-coagulation interactions overwhelm the natural defense systems, catastrophic events occur such as manifested in severe sepsis or inflammatory bowel disease.

EXPRESSION AND REGULATION OF ENDOTHELIAL PROTEIN C RECEPTOR IN MONOCYTE-DERIVED DENDRITIC CELLS.

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Endothelial protein C receptor (EPCR) is a transmembrane protein, homologous to MHC class-1 molecules, that enhances the rate of protein C activation on the endothelial cells of the vessel wall. It has been reported to be present also in polymorphonuclear leucocytes and in monocytes. We showed by immunohistochemistry that dendritic-like cells in the normal gut mucosa express EPCR. We now confirm that these *dendritic-like cells* have a phenotype characteristic of dendritic cells, namely they express CD80, CD83 and HLA-DR. We could not identify EPCR+ dendritic cells in other tissues, such as lymph node, spleen, tonsil, lung, and skin. To further characterize dendritic cell EPCR, we set up cultures of monocyte-derived dendritic cells (MoDCs) that are commonly used as a model of dendritic cell physiology *in vitro*. $CD14^+$ monocytes were separated from buffy coats of healthy donors and cultured for 7 days with IL-4 and GM-CSF to obtain immature DCs. EPCR surface expression was monitored by flow cytometry together with expression of the DC markers HLA-DR, CD1a, CD80 and CD83. After 7 days of culture, approximately 25% of immature DCs expressed EPCR on their surface. De novo expression of EPCR was not correlated with modulation of apoptosis or cell cycle. Lipopolysaccharide-induced terminal maturation of DC down regulated the surface expression of EPCR by 40 % while up regulating the expression of CD83. Incubation