possible we aimed for high relevance, high validity, and low work in terms of the reader's time and effort. We also kept in mind principles of transparency and explicitness. Readers needed to understand where our information came from and how it was assembled.

The first issue of *Clinical Evidence* will contain summaries on the prevention and treatment of about 70 common conditions. Each summary is based on a thorough search and appraisal of the literature, looking for good systematic reviews and, where these are lacking, individual randomised controlled trials. The summaries are written by clinicians with skills in epidemiology and are extensively peer reviewed.

Clinical Evidence joins a growing number of sources of evidence based information for clinicians. But it has several features that, we think, make it unique.

Firstly, its contents are driven by questions rather than by the availability of research evidence. Rather than start with the evidence and summarise what is there, we have tried to identify important clinical questions and then to search for and summarise the best available evidence to answer them.

Secondly, it identifies but does not try to fill important gaps in the evidence. As Jerry Osheroff at the American College of Physicians puts it, *Clinical Evidence* presents the dark as well as the light side of the moon. We feel that it will be helpful for clinicians to know when their uncertainty stems from gaps in the evidence rather than gaps in their own knowledge.

Thirdly, it will be updated every six months. This means that clinicians can rely on it to keep them up to date in the topics that are covered.

Finally, and importantly, it specifically aims not to make recommendations. This is because we feel that simply summarising the evidence will make it more widely applicable. The experience of the clinical practice guideline movement has shown that it is nearly impossible to make recommendations that are appropriate in every situation. Differences in individual patients' baseline risks and preferences, and in the local availability of interventions, will always mean that the evidence must be individually interpreted rather than applied across the board. *Clinical Evidence* provides the raw material for developing locally applicable clinical practice guidelines and for clinicians and patients to make up their own minds on the best course of action. We supply the evidence, you make the decisions.

Our expectation is that *Clinical Evidence* will evolve rapidly in its early years, just as the *British National Formulary* did when it first appeared. Indeed, *Clinical Evidence* may well become a family of products, appearing in different formats (including electronic) and languages for different audiences. In particular, it will evolve in response to the needs of clinicians. We have tried hard to anticipate those needs (not least by involving clinicians at every stage), but it is only when people begin to use *Clinical Evidence* in daily practice that we can know how best to develop it. We hope you will let us know what you think of the sample in this week's journal, and of the first issue of *Clinical Evidence* when it appears later this month.

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Antithrombotic therapy in cancer

Low molecular weight heparins may have a direct effect on tumours

Two recent studies from Scandinavia[1 2] have reinforced the clear association between thrombosis and malignant disease that was first recognised by Trousseau in the 19th century.[3] These population based analyses of cancer risk involved about 86 000 patients with venous thromboembolism, 4200 of whom had cancer. The observed incidence of cancer (especially pancreatic and ovarian) was 1.3 times the expected incidence among the Danish patients with either deep vein thrombosis or pulmonary embolus and 3.2 times the incidence among the Swedish patients. As a corollary, patients with established cancer are at increased risk of venous thromboembolism, which is potentially fatal. Patients with cancer are nearly twice as likely to die of pulmonary embolism in hospital as those with benign disease, and about 60% of these deaths occur prematurely.[4] The hypercoagulable state of malignancy reflects tumour elaboration of tissue factor, the physiological procoagulant.[5] Might antithrombotic treatment help reduce this high risk in patients with cancer?

The risk of thrombosis is further increased when patients receive therapeutic interventions for their cancer. After an abdominal operation the risk of deep vein thrombosis is twice that in non-cancer patients, and the risk of a fatal pulmonary embolus is increased fourfold without routine thromboprophylaxis.[3] Chemotherapy also carries a serious thrombotic risk: the incidence of thrombosis was 9% in a group of postmenopausal women receiving combined chemotherapy and hormonal therapy.[6] Part of this incidence may reflect the route of administration of drugs, since the use of central venous lines in patients with cancer is associated with thrombosis rates of 30-60%.[7] More importantly, by damaging the endothelium, cytotoxic

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chemotherapy releases procoagulants and cytokines which activate the process of coagulation,[5] and it depletes circulating concentrations of naturally occurring anticoagulants such as protein C, protein S, and antithrombin III.

Randomised clinical trials have shown that antithrombotic agents reduce venous thromboembolism in patients with cancer undergoing either operations or chemotherapy. Both unfractionated and low molecular weight heparins lower the risk of deep vein thrombosis after cancer operations.[8] Likewise, oral warfarin reduced the incidence of venous thromboembolism by 85% during chemotherapy for breast cancer.[7] Low molecular weight heparins may be the agents of choice since they have a predictable biological activity after single daily subcutaneous administration, and their safety profile is better than that of unfractionated heparin, with a lower incidence of thrombocytopenia and osteoporosis. Both low molecular weight heparins and low dose warfarin can prevent thrombosis of indwelling central venous catheters in patients with cancer.[7]

For the initial treatment of deep vein thrombosis a standard regimen of intravenous unfractionated heparin and a single daily injection of low molecular weight heparin have proved equally efficacious and equally safe in terms of bleeding.[9] The advantage of low molecular weight heparin is its ease of administration since it can be used in an outpatient setting without the need for laboratory monitoring. However, concerns still exist about the suitability of a fixed dose strategy for the outpatient treatment of deep vein thrombosis in patients with cancer, whose coagulopathy can lead to oscillation between bleeding and massive thrombosis. Specific studies in this population are required to resolve the issue. Recurrent venous thromboembolism is nearly twice as common in patients with cancer who have received oral anticoagulants as in patients without cancer, so low molecular weight heparins may be a better option.

Besides preventing venous thromboembolism, antithrombotic therapy may influence tumour biology. The powerful techniques of in vitro mutagenesis and gene transfer have shown that expression of tissue factor by tumour cells is associated with enhanced growth, metastasis, and angiogenesis.[10] Mechanisms include direct signalling through the tissue factor molecule and the ability of tissue factor to activate blood coagulation and generate downstream serine proteases. Thrombin, the end product of this cascade, may release vascular endothelial growth factor, thereby contributing to tumour angiogenesis.[11] Interference with the activation of coagulation could be a useful antitumour strategy. In patients with small cell carcinoma of the lung both warfarin and unfractionated heparin will prolong survival.[3] An analysis of the original studies of treatment for deep vein thrombosis comparing unfractionated heparin with low molecular weight heparins showed an unexpected 65% reduction in mortality for patients with cancer receiving low molecular weight heparins.[12] A similar survival advantage for low molecular weight heparins has been observed in subsequent studies of deep vein thrombosis, though none of these trials was specifically designed to collect data on cancer prospectively. To clarify the role of low molecular weight heparins in advanced cancer a prospective placebo controlled trial is needed in patients without thrombosis at the time of randomisation.

The role of low molecular weight heparins is already established for preventing and treating thrombosis in patients without cancer, and they are widely applicable in those with malignancy. Besides preventing death from pulmonary embolism, however, low molecular weight heparins offer the possibility of improving survival by a direct effect on the tumour itself. Thus the Trousseau phenomenon could be the Achilles' heel of the carcinoma cell.

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