Research Review Speaker Series™

Venous Thromboembolism and the Cancer Surgical Patient

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This publication is a summary of a recent presentation given by Professor Kakkar at Sebel Pier One, Sydney, Australia, on 22nd September 2011. He discussed the burden of venous thromboembolic (VTE) disease and rationale for primary thromboprophylaxis in the perioperative period, the role of extended prophylaxis into the post-discharge period, guidelines, and the impact of VTE on the outcome of patients with malignant disease.

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Lord Kakkar completed his medical education at King's College Hospital Medical School, University of London, and was awarded an MBBS in 1988 and a PhD in 1998 from Imperial College London. He was made a fellow of the Royal College of Surgeons of England in 1992.

Lord Kakkar's research interests include the prevention and treatment of venous and arterial thromboembolic disease and cancer-associated thrombosis. His awards include Hunterian Professor, Royal College of Surgeons of England 1996, David Patey Prize, Surgical Research Society of Great Britain and Ireland 1996, Knoll William Harvey Prize, International Society on Thrombosis and Haemostasis 1997, James IV Association of Surgeons Travelling Fellow 2006 and Wellcome Memorial Lecture, Royal Society of Medicine 2009.

Professor the Lord Kakkar was created a life peer in 2010 and sits on the cross benches of the House of Lords.

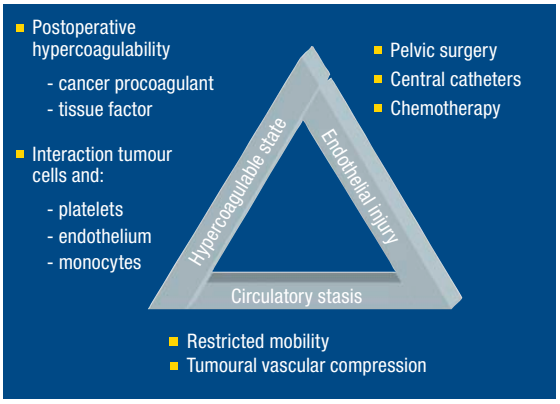
Burden of disease

Trousseau was the first to recognise the important association between thrombosis and malignant disease.[1] He observed that patients presenting with gastrointestinal (GI) symptoms and thrombophlebitis could immediately be diagnosed as having cancer as the underlying cause of those GI symptoms. Since that time, numerous studies have confirmed this association.

Rudolph Virchow described the pathophysiological basis for the development of VTE.[2] He proposed that three elements – hypercoagulability, vessel wall injury, and venous stasis – were the major factors responsible for the development of an intravascular thrombus (Figure 1). The pathogenesis of VTE in patients undergoing operation for cancer may be described in the context of Virchow's triad. Tumours elaborate procoagulant molecules that shed into the circulation and are able to activate blood coagulation beyond the trauma seen with surgical intervention. In response to the cancer, host cells are activated that shed microparticles into the circulation, thereby activating blood coagulation. Venous stasis occurs in patients enduring a prolonged period on the operating table and during postoperative recovery from major surgery. Large tumours, particularly in the pelvis, will compress vessels and reduce blood flow in the deep veins of the lower limb. It is known that the use of central venous catheters and, in particular, systemic chemotherapy, is associated with endothelial damage, changing its phenotype from an anticoagulant phenotype to a procoagulant phenotype.

Evidence demonstrates that the coagulation system is activated in patients with malignant disease. Kakkar and colleagues examined activation of the coagulation system in 106 cancer patients and 72 healthy volunteers by measuring plasma levels of tissue factor (TF), Factor VIIa, Factor XIIa, thrombin-antithrombin complex (TAT), and prothrombin fragments 1+2 (PF 1+2).[3] Higher levels of all five indices were found in the cancer patients compared with the controls. In particular, TF levels were 67% higher and Factor VIIa levels were 46% higher in the patients with cancer. This study indicates that, prior to intervention with surgery, chemotherapy or radiotherapy, these patients are profoundly hypercoagulable.

Figure 1 **Virchov's triad**[2]



When Kakkar and colleagues examined the expression of TF in 55 specimens of ductal adenocarcinoma of the pancreas, 20% of the well-differentiated and nearly 80% of the poorly-differentiated anaplastic tumours showed strong expression for TF.[4] Conversely, no TF expression was detected in ductal epithelium from normal pancreas. Subsequently, technology has demonstrated that tumours may shed TF in phospholipid-rich microparticles that can then activate circulating Factor VIIa, which subsequently activates Factor X in the coagulation cascade. Equally, TF acts as a signalling receptor in epithelial tissue, enhancing the metastatic potential for tumour cells in the experimental situation and the ability to generate angiogenesis. Thus, TF appears to have a very important role, as do receptors for other coagulation proteases, particularly activator Factor II thrombin.

The overall incidence of postoperative deep vein thrombosis (DVT) in patients with cancer who have undergone major abdominal surgery without thromboprophylaxis has been shown to be about twice as high as that of non-cancer patients (37% vs 20%).[5] In an analysis of data encompassing a 10-year period, the incidence of post-operative pulmonary embolism (PE) was remarkably higher in patients with cancer than in those without cancer (~2.3% vs 0.3%; OR 6.7).[6] Even among patients on the medical ward, the risk of developing PE is 7 times higher for cancer patients compared with non-cancer patients (0.73 vs 0.10; OR 7.3).

Researchers have examined the reported frequency of VTE as a complication after discharge from hospital in a large administrative database from California.[7] Regardless of the anatomical site of operation, surgery for malignant disease was associated with a higher reported rate of thromboembolic complications in the 90-day discharge period compared with surgical procedures without the presence of cancer.

A large prospective registry of 2,373 patients who had undergone laparotomy for abdominal or pelvic malignancy was followed for 30 days postoperatively and demonstrated that the following factors were associated with a greater risk for the development of VTE in the cancer setting: age over 60 years (OR 2.63); previous VTE (5.98); operation lasting >2 hours (4.50); advanced cancer (2.68); and ≥4 days postoperative bed rest (4.37).[8] The odds ratios were in the range of 2.6 and 6, depending on the factor in question.

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Rationale for thromboprophylaxis

The natural history of DVT in postoperative general surgical patients provides evidence for the efficacy of interventions to prevent DVT and, ultimately, PE. In a study conducted in 1969, in which patients received no prophylaxis and no treatment for silent DVT, fibrinogen leg scanning revealed that the majority (92) of the 132 postoperative patients had no evidence of an abnormality.[9] In 40 patients, there was evidence of an early thrombus in the calf veins, 26 of whom continued to demonstrate a thrombus in the calf veins postoperatively and 9 subsequently propagated a thrombus from the calf to the proximal veins, 4 of whom developed PE. These data are firstly important for showing the natural history of VTE, how DVT is related to PE, and secondly, they demonstrate that a surrogate end point, silent DVT, may be used to determine the efficacy of interventions to prevent DVT and PE.

Leg scanning by means of iodine-125-labelled fibrinogen was also used to explore the potential of a new method at that time of a low-dose unfractionated heparin (UFH; 5000 U subcutaneously twice daily) commencing 2 hours prior to operation and continued postoperatively for 7 days.[10] The study revealed that 42% of controls developed DVT in the postoperative period, versus only 8% of the heparin group. However, surgeons remained skeptical about exposing large numbers of patients to heparin prophylaxis, without any clear demonstration that this intervention would reduce the frequency of fatal PE.

In 1975, a landmark multinational trial randomised 4,121 patients undergoing major surgery to a control group (no heparin) or to low-dose UFH commenced preoperatively and continued 3 times daily postoperatively for around 7–10 days or until the patient was mobile.[11] The study end point was autopsy-proven fatal PE, with about 70% of patients who died in the study period undergoing autopsy. Whereas 16 patients in the control group died of autopsy-proven fatal PE in the postoperative period, only 2 of the UFH group did so ($p<0.005$), indicating that small prophylactic doses of heparin therapy in the perioperative period could save 7 lives for every 1,000 operated patients. Such therapy therefore has an important role on improving overall outcome from operation. Notably, of the 23% of patients (n=953) who were randomised with malignant disease, 1.6% of the controls died of fatal PE versus 0.4% of the UFH group.

When data were examined as to bleeding complications, no significant between-group differences were observed for excessive blood loss, mean transfusion requirement, or mean haemoglobin (Hb) fall, although numerically there were more patients in the UFH group than in the control group for those three end points. However, there was a significant increase in the reported frequency of wound haematoma (117 controls vs 158 UFH recipients; $p<0.01$). Prof. Kakkar suggests that the potential risk for a small increase in bleeding complications should be weighed against the demonstrated substantial reduction in mortality associated with fatal PE. Overall, the balance of data strongly favours pharmacological prophylaxis for high-risk surgical patients in the perioperative period, with evidence showing that it reduces both DVT and fatal PE.[12-16]

A meta-analysis in 1988 of all trials that had randomised patients to heparin or to no antithrombotic therapy in the perioperative period demonstrated that there was not only a reduction in fatal PE (by about two-thirds) in all clinical emboli, but there was even an effect on other causes of death, principally a reduction in other cardiovascular causes of death, in favour of prophylaxis.[17] When the data are considered across all of these studies, in a population of around 12,000 patients, no between-group difference is seen in the incidence of fatal bleeds. Prof. Kakkar considers these data to be important, as they put into perspective the benefits of prophylaxis against the potential harm. It is important not to ignore potential bleeding complications but to be sensitive to the fact that in avoiding prophylaxis unnecessarily, patients might be put at great risk for developing fatal PE.

In the last 15 years, the low-molecular-weight heparins (LMWHs) have been favoured over low-dose UFH for perioperative thromboprophylaxis. In one of the first studies to investigate the optimal dose of LMWH in patients undergoing laparotomy for malignant and benign abdominal disease, the treatment options were dalteparin 2,500 IU (a dose advocated for general surgical procedures) or dalteparin 5,000 IU (a dose used in patients undergoing elective hip arthroplasty).[18] In this trial of 2,070 patients, two-thirds of whom were undergoing laparotomy for cancer, venography screening for postoperative DVT on Day 10 revealed a significantly lower incidence of DVT in the higher-dose LMWH group in the cancer surgical population (8.5% vs 14.9% of the lower-dose LMWH group; $p<0.001$). Whereas doubling the dose of LMWH did not significantly increase the risk of bleeding complications in the group with cancer (4.6% vs 3.6%), doubling the dalteparin dose doubled the frequency of bleeding complications in the patients without cancer (4.7% vs 2.7%; $p=0.02$). This suggests that the cancer patients are profoundly hypercoagulable and require higher doses of an antithrombotic agent to achieve the best possible degree of prophylaxis. The lack of an association with bleeding may be because this high level of hypercoagulability neutralises much of the administered thrombotic agent.

In a meta-analysis of 48,000 patients from randomised controlled trials including both cancer and non-cancer general surgery populations comparing once-daily LMWH with three times daily low-dose UFH, whichever end point was evaluated (whether screen-detected DVT through to clinical events), once-daily LMWH was as effective as three times daily UFH.[19] As regards safety parameters, bleeding complications are equal between the two strategies, with a suggestion that wound haematomas are reported less frequently in clinical trials where cancer patients have received LMWH.

Prof. Kakkar noted that there are circumstances in surgical practice where it would be inappropriate to consider using pharmacological prophylaxis, in particular, where patients are actively bleeding or where there is a very high risk of bleeding complications, particularly complications that would manifest themselves with devastating consequence. In these circumstances, mechanical methods may be used. Scant data exist for mechanical methods of prophylaxis (i.e., passive, including compression stockings or active, such as pneumatic calf suppression or electrical calf stimulation). A UK-based health technology assessment that included all patient populations and all methods of compression in a single analysis demonstrates that when the data are added together, it is reasonable to conclude that DVT is reduced by about 67% where mechanical methods are used as monotherapy.[20] However, when considering PE, potentially because there are fewer data, less robust methodology in the trials and fewer patients, it is not possible to demonstrate that mechanical prophylaxis reduces the frequency of PE significantly and to such an extent that mechanical methods may confidently be advocated as monotherapy for the prevention of postoperative thromboembolic disease. Under these circumstances, the general guidance is that they be used as monotherapy where pharmacological intervention is contraindicated.

Kakkar and colleagues compared the efficacy of heparin prophylaxis (either a LMWH once daily or low-dose UFH three times daily) in the prevention of VTE in 23,078 non-cancer and cancer surgical patients.[21] The primary study end point was death within 10 days of discontinuation of prophylaxis and the frequency of autopsy-proven fatal PE. While there were no differences between the two strategies for the primary end point, a secondary analysis that examined outcome by indication for operation revealed that autopsy-confirmed fatal PE was significantly more frequent among the cancer patients (0.33% [20/6,124]) than in non-cancer patients (0.09% [15/16,954]; $p=0.0001$), despite the use of heparin prophylaxis for the duration of hospital stay.

Prof. Kakkar speculates whether the natural history of VTE resembles the phenomenon demonstrated in patients undergoing elective hip arthroplasty, with two peaks in the development and presentation of the disease – one occurring early after the operation and one some days or weeks later.[22] In hip arthroplasty, a number of studies have evaluated this question, including one by Kakkar and colleagues, in which patients were randomised to one of two strategies: one that provided LMWH for 10 days while in hospital after hip arthroplasty, or an extended-duration strategy involving 35 days of an orally active anticoagulant agent.[23] An analysis of rates of symptomatic VTE between the day of operation and Day 35 (prior to venography) revealed that as soon as prophylaxis was stopped in the short-duration treatment arm, patients started to present with symptomatic VTE. This phenomenon was not seen in the extended-duration prophylaxis group.

In a population of general surgery patients, about 20% to 25% of the total PE burden presented after discharge from hospital.[6] In Italian data from 2,373 patients operated for cancer (general abdominal, gynaecology, and urology) who were followed for 30 days, 2.1% of patients developed symptomatic VTE by Day 30 despite the use of prophylaxis in hospital, and of the 1.7% of patients who died, death was attributed to thromboembolic disease in 46%.[8] It therefore appears to be an important problem. In an analysis of the presentation of those symptomatic thrombi, VTE cases tailed off after Day 15 and there was a resurgence of VTE between Days 21 and 30, resulting in 40% of VTEs occurring more than 21 days after cancer surgery.[8] Thus, there is a suggestion that the presentation of thrombosis that we see after hip arthroplasty may be similar in patients after abdominal surgery for malignant disease.

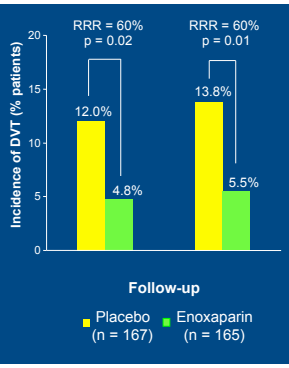
Role of extended prophylaxis

Clinical trials have addressed whether extending prophylaxis would be beneficial in this population. Typically, patients are randomised prior to operation to a short or extended duration of thromboprophylaxis, with all patients receiving a LMWH while in hospital and then at the time of discharge either continuing with the LMWH or placebo or are randomised to a control group. Venography on Day 30 is used to evaluate the total burden of asymptomatic thrombi.

The first study to explore this outcome was the ENOXACAN II trial, involving 332 patients, the majority of whom underwent operation with curative intent for colorectal malignancy (see Figure 2).[13] Extending prophylaxis was associated with a 60% risk reduction for DVT at Day 30 venogram. In the short-duration group, DVTs occurred in 12% of placebo recipients versus 4.8% of patients given extended prophylaxis into the post-discharge period. The benefits of those 30 days of extended prophylaxis were maintained up to 3 months of clinical follow-up.

Figure 2 Outcomes from ENOXACAN II[13]

- 332 patients undergoing surgery for abdominal or pelvic tumours received enoxaparin (40 mg q.d.) for 1 week followed by enoxaparin or placebo for another 21 days
- Venography was performed at 30-day and 3-month follow-up
- At each follow-up, prolonged TP was associated with a 60% risk reduction for DVT



In the FAME trial, a subgroup of 165 patients in the prolonged prophylaxis group who had undergone laparotomy for cancer demonstrated a similar benefit – a 55% risk reduction for VTE on Day 30 and, interestingly, a 77% risk reduction for proximal DVT; i.e., those thrombi confined to the iliofemoral or iliac segments, the thrombi of highest concern in relation to the potential development of PE.[24]

A meta-analysis that included both patients who have undergone abdominal surgery for malignant disease and other high-risk abdominal surgical procedures has demonstrated an approximately 55% reduction in total VTE, a 55% reduction in DVT and a 76% reduction in proximal DVT in favour of extended prophylaxis, without any difference in bleeding complications associated with extended prophylaxis.[25]

The more recent, similarly designed CANBESURE study included 703 patients given short-duration prophylaxis for 1 week followed by placebo or extended-duration LMWH prophylaxis (bemiparin 3500 IU) for about 28–30 days.[26] At 30 days, bilateral venography was performed in both groups. Extended prophylaxis reduced the incidence of major VTE (defined in venous thrombosis prophylactic studies as a composite of proximal DVT, non-fatal PE and VTE-related deaths) by 82.4% and major VTE plus symptomatic DVT by 73.6%.[27] Total DVT (principally driven by asymptomatic calf thrombi) was reduced by just 36%, while proximal DVTs were reduced by nearly 90%. No significant between-group difference was observed in major bleeding complications, although numerically there were more in the extended-duration group (0.6% vs 0.3% in the short-duration prophylaxis group).

These data consistently demonstrate that the thrombi that are most frequently reduced with extended prophylaxis in the cancer surgical population appear to be proximal vein thrombi, and that if there is an increase in bleeding associated with extended prophylaxis, it appears to be small. Prof. Kakkar described this as intuitive, bearing in mind that the extra prophylaxis is provided after 7 days of standard prophylaxis in hospital; only a small risk for bleeding would be expected in that much later postoperative period.

Guidelines

The American Society of Clinical Oncology (ASCO) guidelines were the first to issue recommendations for VTE prophylaxis in surgical cancer patients.[28] At the time, the ASCO group considered that all patients in the perioperative period, while confined to bed in hospital, should receive prophylaxis with a heparin or LMWH, commencing preoperatively and continuing at least for the duration of hospital stay. In addition, for a group of patients defined in the guidelines as high risk (i.e. residual tumour burden, a previous history of VTE, obesity), should have extended prophylaxis for up to 4 weeks postoperatively. Subsequently, other guidelines groups have adopted similar recommendations.[22,29,30]

Prof. Kakkar predicts that when the ASCO guidelines are updated with the increasing data now available for the benefits of extended prophylaxis these recommendations will become stronger, in terms of advocating a potential benefit for extended prophylaxis in patients who have undergone a laparotomy for abdominal or pelvic malignancy.

Impact of VTE

Prof. Kakkar evaluated the potential impact of VTE and overall survival in cancer patients, using US data presented at ASCO in 2009.[31] After adjusting for all confounding variables affecting survival, these data show that over the course of the patients' malignant disease, those presenting with thrombosis have a 3-fold higher mortality risk compared with those who have never developed a thrombosis (HR 3.04; 95% CI 1.31 to 7.15; $p<0.01$).

Prof. Kakkar commented that while these results must be interpreted with care, many other datasets present the same finding, i.e., the presentation of thrombosis with cancer is associated with a poorer overall outcome. These data are somewhat speculative and an explanation is difficult. In Prof. Kakkar's view, there are potentially three explanations:

- Firstly, patients that develop VTE have aggressive tumours that biologically are programmed to kill the patient and that the development of thrombosis merely represents a surrogate for that very nasty type of cancer and trying to prevent thrombosis would be meaningless, in terms of ultimately affecting the outcome of the patient.
- The second explanation might be that after developing a first thromboembolic event, a patient is at greater risk of recurrent thromboembolism. Cancer patients who develop their first thrombosis have a 3-fold greater risk of recurrent VTE compared to non-cancer patients with thrombosis. As autopsies are no longer performed on these patients, it may be that the recurrent thrombosis in cancer patients is more likely to be fatal PE, which is unrecognised without autopsy. Thus, it would be advisable to avoid the first thrombosis, in order to reduce the risk of subsequent recurrent thrombosis, which might manifest itself as PE.
- The third potential explanation, which is supported by experimental data at a molecular level, could be that once patients develop thrombosis, the active thrombus will generate really large quantities of coagulation proteases. These can find themselves in the peritumour environment and will stimulate receptors expressed in tumours that are sensitive to activated Factor X, activated Factor II and VII, and so on. Ultimately, the activation of those receptors will change the phenotype of the cancer to make it more aggressive and patients die earlier. Under those circumstances, it would seem intuitive to try to prevent thrombosis if ultimately there is a biological relationship between the thrombus and the behaviour of the tumour.

Another set of US-based data (the California Cancer Registry linked to the California Patient Discharge Data Set) has been used to calculate the hazard of death in the first year after thromboembolism diagnosis for patients with different tumour types initially presenting with different stages of disease (locally-defined disease, disease that has spread to regional lymph nodes, or true metastatic disease) between 1993 and 1995 (see Figure 3).[32] The data suggest that the adverse impact of thrombosis associated with outcome from malignant disease is worse in early-stage disease patients for a certain tumour type (e.g., breast cancer, ovarian cancer) than in those with more advanced disease. Prof. Kakkar suggested that it is reasonable to focus on trying to prevent thrombosis, if possible, in these patients. However, he stressed that these data are speculative and must not be over-interpreted.

Figure 2 Outcomes from ENOXACAN II[13]

- 332 patients undergoing surgery for abdominal or pelvic tumours received enoxaparin (40 mg q.d.) for 1 week followed by enoxaparin or placebo for another 21 days
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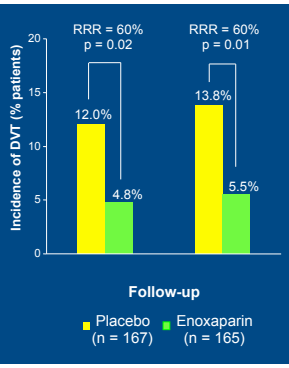

Conclusions

- Primary prophylaxis mandatory for patients undergoing laparotomy for cancer
- Increasing evidence for the benefits of extended post-discharge LMWH
- VTE associated with poor clinical outcome

Q&A session

Q: What dose of anticoagulant should be administered to a 240 kg patient undergoing surgery for malignancy?

A: Do you change the dose of LMWH if operating on obese patients? In general obesity, no. The only area where it is advocated (and is backed by reasonable case series evidence) is in bariatric surgery, where the advice is to double the dose of enoxaparin from 40 mg once daily to 40 mg twice daily. This dose would probably be appropriate for this very large patient.

Q: The Westmead Hospital gynaecological unit has adopted extended prophylaxis for the gynaecological cancer patients, who have done well on this schedule without an increase in bleeding events. When should the first dose of prophylaxis be given? These patients are invariably given an epidural and therefore do not receive a preoperative dose. How important is this? Secondly, in the case of a 240 kg woman with some postoperative bleeding, how long can postoperative prophylaxis be delayed before losing all potential benefit?

A: The purist's approach would say that there is no evidence that commencing prophylaxis postoperatively in general surgical patients is effective. A study by Kakkar and colleagues compared a preoperative regimen with a postoperative regimen starting 8 hours after operation, in a large cohort of 4,400 patients, 80% of whom were having laparotomy for cancer. The postoperative regimen was inferior to preoperative prophylaxis, as regards the frequency of DVT. The timing issue can be dealt with in two ways: by administering the dose 10–12 hours prior to operation (the pre-assessment clinic can teach patients how to self-inject, so that they can dose themselves at home the night prior to hospital admission). The second option is allow the epidural to be placed and administer a dose of LMWH before making the incision. In the event of worrisome bleeding, if the patient has received a preoperative dose, Prof. Kakkar tends to delay giving his evening of operation dose until the morning of the first postoperative day. For the 240 kg patient, Prof. Kakkar would opt for a mechanical method postoperatively (pneumatic calf suppression), although he cautions that mechanical methods must be used with care under such circumstances. Clinical judgement is necessary.

Q: Does the mode of surgery make a difference? (i.e. laparoscopy vs laparotomy?)

A: Current advice is to provide the same prophylaxis for an open procedure as for a procedure performed laparoscopically.

Q: It appears that it is the disease, not the modality of the operation, which makes the difference.

A: Yes. Prof. Kakkar believes it would be wrong to give anything other than the same prophylaxis and this is supported by the guidelines.

Q: Can data on oral vs injectables in hip and knee replacement surgery be extrapolated to general surgery?

A: Prof. Kakkar would be reluctant to do so. Firstly, in the postoperative period, giving all oral antithrombotic therapy would be unwise; a number of patients are nil by mouth, and absorption is impacted to varying degrees in other patients. The early postoperative dosing is vitally important for preventing VTE, because the majority of thrombi are initiated while the patient is on the operating table. A subcutaneous dose ensures absorption.

Q: What is the optimum time to give a dose prior to surgery if you are not worried about an epidural? Secondly, is there any evidence for extended prophylaxis in patients having major abdominal surgery that is not for cancer?

A: With low-dose UFH, the optimum time is 2 hours prior to surgery. LMWH is best given at either 10–12 hours prior to surgery, in a 40 mg dose, or as 20 mg 2 hours before surgery. Clinical data are scant as to extended prophylaxis in patients undergoing major abdominal surgery that is not cancer-related; Prof. Kakkar advises clinical judgement.

Q: In the palliative care of metastatic cancer, patients are at significant risk of thromboembolism. How should they be treated?

A: In a study recently completed by Prof. Kakkar and colleagues of 3,200 patients receiving palliative chemotherapy for locally advanced or metatastic cancer, who were randomly allocated to a placebo or an ultra-low molecular weight heparin. Over an average of about 3 cycles of chemotherapy, the ultra-low dose was associated with a 65% reduction in symptomatic VTE (about 3.6% vs 1.2%). Other data from the palliative care community have considered whether it is reasonable to try to prevent thrombosis. Because a DVT is associated with pain, swelling, discomfort, the need for more anticoagulation and more analgesia, some clinicians advocate providing prophylaxis until the late hospice stage. When to stop the prophylactic therapy is a difficult question and must be left to clinical judgement.

Professor Kakkar has provided research support for and been a principal investigator in Bayer HealthCare, sanofi-aventis, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Eisai. He has served as a Consultant for Bayer HealthCare, sanofi-aventis, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, Eisai, Aryx Therapeutics, and Canyon.

Professor Kakkar has been a member of Scientific Advisory Boards of Bayer HealthCare, sanofi-aventis, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Eisai. He has accepted Honoraria from Bayer HealthCare, sanofi-aventis, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, Eisai, and GlaxoSmithKline.

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