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Venous Thromboembolism Prophylaxis in Cancer Patients

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1. Introduction

Venous Thromboembolism (VTE) is a common disease, comprising the life-threatening pulmonary embolism (PE) and its precursor deep vein thrombosis (DVT). In view of the clinically silent nature of VTE; the incidence, prevalence and mortality rates are probably under estimated (Kniffin et al., 1994). Although VTE is a common disease, fortunately it is preventable; identifying high risk patients and the application of suitable prophylactic measures is the best way to decrease the incidence of VTE and its associated complications. Using unfractionated heparin (UFH), the rate of radiologically detected DVT was reduced by 67% without significant bleeding complications (Belch et al., 1981).

Although most patients survive DVT, they often suffer serious and costly long-term complications. Venous stasis syndrome (postphlebitic syndrome) with painful swelling and recurrent ulcers is well known complication following DVT (Prandoni et al., 1996). Additionally, PE is associated with substantial morbidity and mortality both tend to be higher among cancer patients and those who survive such event may develop chronic complications like pulmonary hypertension (Carson et al., 1992; Pengo et al., 2004). In a large study, Sørensen et al. examined the survival of patients with cancer and VTE compared to those without VTE matched for many factors including the type and duration of cancer diagnosis; the one year survival rate for cancer patients with VTE was 12% compared to 36% in the control group ($P<0.001$). Furthermore, the risk of VTE recurrence was higher in cancer patients compared to those without (Sørensen et al., 2000).

2. Cancer as a risk factor for VTE

The association between cancer and thrombosis is well-established since the first observation made by Armand Trousseau more than hundred years ago (Prandoni et al., 1992). Cancer and its treatment are recognized risk factors for VTE; in a population-based case-control study of 625 Olmsted County patients, the risk of VTE was six- fold higher in cancer patients compared to those without (Heit et al., 2000). Thrombosis is the most frequent complication and the second cause of death in patients with overt malignant diseases. Increasing evidence suggests that thrombotic episodes may also precede the diagnosis of cancer by months or years (Donati, 1995). The risk of VTE varies by cancer type; higher in patients with malignant brain tumors and adenocarcinoma of the pancreas, colon,

stomach, ovary, lung, prostate, and kidney (Chew et al., 2006; Gerber DE, et al., 2006; Marras et al., 2000; Sallah et al., 2002; Thodiyil& Kakkar, 2002), but lower in sites like skin and breast (Andtbacka et al., 2006; Chew HK et al., 2007). In addition to primary tumor type, other cancer-related factors play important role in VTE rates; the risk of VTE is highest during the first 3–6 months after the initial diagnosis of cancer (Blom et al., 2005). Such risk also varies with the stage of the disease; much higher with advanced stage compared to early stage disease (Blom JW et al., 2005) and among cancer patients on active treatment with chemotherapy or radiotherapy (Haddad & Greeno, 2006).

Certain anti-cancer therapies are known to increase the risk of VTE in cancer patients. The rate of VTE increases by two to five folds in women with breast cancer treated with tamoxifen, a selective estrogen receptor modulator (SERM), and this risk was even higher when tamoxifen was combined with chemotherapy, a practice that was abandoned many years ago (Fisher et al., 2005; Pritchard et al., 1996). Aromatase inhibitors (AI), however, like anastrozole, letrozole and exemestane are less thrombogenic (Breast International Group (BIG) 1–98 Collaborative Group, 2005; ATAC (Arimidex Tamoxifen Alone or in Combination Trialists' Group), 2002).

Cancer type:
High: Brain, Ovary, Pancreas, Colon, Stomach, Lung, Prostate, Kidney
Low: Skin, Thyroid, Breast
Duration since cancer diagnosis:
High: First 6 months
Low: After 12 months
Stage of disease:
High: Locally-advanced and metastatic disease
Low: Early-stage
Anticancer therapy:
High: Chemotherapy, radiotherapy, surgery
Low: No active treatment
Hormonal therapy:
High: Tamoxifen
Low: Aromatase inhibitors like letrozole, anastrozole and exemestene
Antiangiogenesis and immune modulators:
Thalidomide
Lenalidomide
Bevacizumab
Sorafenib
Sunitinib

Table 1. Cancer-related risk factors for thrombosis

The recent introduction of immune modulators and antiangiogenesis drugs in clinical practice resulted in higher rates of VTE among cancer patients receiving such therapy. Thalidomide, lenalidomide, bevacizumab, sorafenib and sunitinib are approved by the US Food and Drug Administration (FDA) for many types of cancers; all are associated with increased risk of VTE (Zangari et al., 2009). Up to 23% of patients using bevacizumab in combination with chemotherapy to treat colorectal and gastric cancers experienced

thrombotic events (Kabbinavar et al., 2007; Shah et al, 2005). Lower rates, however, wereobserved when different combination chemotherapy were used in the treatment of non-small cell lung cancer (Johnson et al., 2004). In addition to thrombosis, bevacizumab was associated with significant increase risk of bleeding; a fact that complicates decision making (Kabbinavar et al., 2003) . However, the highest incidence of VTE was observed in multiple myeloma patients treated with thalidomide, dexamethasone and doxorubicin-containing chemotherapy [Zangari et al., 2002). Higher VTE rates were also observed with thalidomide derivatives; lenalidomide and pomalidomide when used in combination with dexamethasone (Zonder et al., 2006 & Dimopoulos et al., 2007). Cancer-related risk factors are summarized in table-1.

Different antithrombotics including low molecular weight heparin (LMWH), low-dose warfarin, full-dose warfarin with target international normalized ratio (INR) of 2 to 3, and aspirin (ASA) were all tried to reduce the risk of VTE in cancer patients undergoing such therapy (Baz et al., 2005; Cavo M et al., 2004; Minnema et al., 2004). Specific recommendations in these clinical settings are beyond the scope of this review. However, in a recent trial that included a total of 667 patients with previously untreated multiple myeloma who received thalidomide-containing regimens and had no clinical indication or contraindication for a specific antiplatelet or anticoagulant therapy were randomly assigned to receive ASA (100 mg/d), fixed-dose warfarin (1.25 mg/d), or LMWH (enoxaparin 40 mg/d). A composite primary end point included serious thromboembolic events, acute cardiovascular events, or sudden deaths during the first 6 months of treatment; of 659 analyzed patients, 43 (6.5%) had serious thromboembolic events, acute cardiovascular events, or sudden death during the first 6 months (6.4% in the ASA group, 8.2% in the warfarin group, and 5.0% in the LMWH group). Compared with LMWH, the absolute differences were +1.3% (95% CI, - 3.0% to 5.7%; *P* =.544) in the ASA group and +3.2% (95% CI, - 1.5% to 7.8%; *P* = .183) in the warfarin group (Palumbo et al., 2011).

In addition to chemotherapy agents, drugs that are commonly used to support cancer patient while on active treatment may increase the risk of VTE. Erythropoiesis-stimulating agents (ESA); erythropoietin and darbepoietin are both associated with higher VTE rates. A meta-analysis of 35 trials in 6,769 cancer patients concluded that such treatment increased the risk of thromboembolic events by 67% compared with patients not receiving this therapy (Bohlius et al., 2006).

3. Making the decision

Despite its proven success, many registry studies have shown low compliance rates with published VTE prophylaxis guidelines. In a national Canadian multi-center survey study (the CURVE study), the medical records of patients in 20 teaching and 8 community hospitals were reviewed to assess the adherence to the established sixth American College of Chest Physicians (ACCP) consensus guidelines for VTE prophylaxis. In this study, 1894 eligible patients were included; thromboprophylaxis was administered only to 23% of all patients and to 37% of patients who were bedridden for more than 24 hours. However, only 16% of the patients had appropriate prophylaxis; in particular, patients with cancer had a significantly reduced likelihood of receiving prophylaxis (OR = 0.40, 95% CI (0.24–0.68)

(Kahn et al., 2007). Similar findings were also reported in the IMPROVE study in which only 45% of cancer patients who either met the ACCP criteria for requiring prophylaxis or were eligible for enrollment in randomized clinical trials that have shown the benefits of pharmacologic prophylaxis actually received prophylaxis [Tapson et al., 2007]. In another study conducted by our group, two hundred cancer patients with established diagnosis of VTE were identified; majority (91.8%) had advanced-stage cancer at time of VTE diagnosis. In addition to cancer, many patients had multiple coexisting risk factors for VTE with 137 (68.5%) patients had at least three, while 71 (35.5%) had four or more. Overall, 111(55.5%) patients developed lower-extremity DVT while 52 (26%) patients developed PE, other sites accounted for 18%. Almost three quarters of the patients (73.5%) had not received any antecedent prophylaxis. Prophylaxis rate was 23% among patients with >3 risk factors and 50% among the highest risk group with >5 risk factors (Abdel-Razeq et al., 2011).

Compared to surgical patients, decisions on when to offer prophylaxis in cancer patients admitted to medical units is difficult to make (Monreal et al., 2004); medical patients typically have many risk factors, the interaction of which is difficult to quantify. In a recent survey, The Fundamental Research in Oncology and Thrombosis (FRONTLINE), marked differences were seen in the use of thromboprophylaxis for surgical and medical cancer patients, with over 50% of surgeons reporting that they initiated thromboprophylaxis routinely, while most medical oncologists reported using thromboprophylaxis in less than 5% of medical cancer patients (Kakkar et al., 2003). These studies and many others (Chopard et al., 2005; Ageno et al., 2002), demonstrate that VTE prophylaxis in cancer patients is still underutilized.

Many factors may contribute to the low VTE prophylaxis rate in cancer patients. Obviously, concerns about bleeding especially in patients undergoing active treatment with chemotherapy that can lead to low blood counts is one of these reasons; this issue was evident in our study patients where 113 (18.6%) had prolonged PT and or PTT and another 92 (15.2%) had platelet counts < 100 K (Abdel-Razeq et al., 2001). While these may not represent absolute or even relative contraindications for using anticoagulants for VTE prophylaxis, nevertheless, such factors may prevent physicians from prescribing anticoagulant prophylaxis for cancer patients. Other reasons may include concerns about higher bleeding risks from tumor metastasis in vital structures like the brain. Such patients can be offered mechanical methods if anticoagulants deemed contraindicated. However, the absence of a suitable risk assessment model may also contribute to such low prophylaxis rate; such risk assessment model should take into account the additive or even the synergistic effect of the many other additional risk factors that cancer patients are typically admitted with.

Caprini et al. had established a risk assessment model to help health professionals in making the decision on when and how to prescribe VTE prophylaxis (Caprini et al., 2001 ; Motykie et al., 2000). Though we found it useful, we faced several limitations when we tried to apply such model in cancer patients. All cancer patients were given the same risk score; while in fact type of cancer, stage, nature of anti-cancer therapy and time since cancer diagnosis are, as discussed above, important factors that affect VTE rate in cancer patients (Abdel-Razeq et al., 2010).

4. Published guidelines

Several clinical and scientific groups including the ACCP (Geerts et al., 2008), the American Society of Clinical Oncology (ASCO) (Lyman et al., 2007) and the National Comprehensive Cancer Network (NCCN) (Wagman et al., 2008) have established guidelines for VTE prophylaxis in cancer patients. All have different and somewhat conflicting recommendations but all lack a risk assessment model. While the ACCP guidelines were very conservative and advised prophylaxis for cancer patients who are bedridden with an acute medical illness, the NCCN, on the other hand, lowered their threshold for VTE prophylaxis; their most recent updated guidelines stated: ''The panel recommends prophylactic anticoagulation therapy for all inpatients with a diagnosis of active cancer (or for whom clinical suspicion of cancer exists) who do not have a contraindication to such therapy (category 1).'' Their recommendation was based on an assumption that ambulation in hospitalized cancer patients is inadequate to reduce VTE risk (Wagman et al., 2008). The ASCO guidelines published in 2007 have taken a more neutral position by stating in their summary conclusions: "Hospitalized patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants in the absence of bleeding or other contraindications to anticoagulation" (Lyman et al., 2007).

5. Ambulatory cancer patients

Cancer patients treated in the outpatient setting can also be at high risk for VTE. Current guidelines do not recommend anticoagulant prophylaxis for ambulatory cancer patients. Khorana et al tried to establish a risk assessment model for VTE prophylaxis in ambulatory cancer patients after the initiation of chemotherapy. Five predictive variables were identified in a multivariate model: site of cancer (2 points for very high-risk site, 1 point for high-risk site), platelet count of 350 x 10^9/L or more, hemoglobin less than 100 g/L (10 g/dL) and/or use of erythropoiesis-stimulating agents, leukocyte count more than 11 x 10^9/L, and body mass index of 35 kg/m^2 or more (1 point each). Rates of VTE in the validation part of their study were 0.3% in low-risk (score = 0), 2.0% in intermediate-risk (score = 1-2), and 6.7% in high-risk (score $\geq$3) category over a median of 2.5 months. The application of this model can identify patients with a nearly 7% short-term risk of symptomatic VTE and may be used to select cancer outpatients for studies of thromboprophylaxis (Khorana et al., 2008).

More recently, researchers focused on biomarkers that can predict the occurrence of VTE. P-selectin, found in the α granules of platelets and endothelial cells and expressed on the cell surface on activation, mediates the adhesion of leukocytes, platelets, and cancer cells in inflammation, thrombosis, and cancer growth and metastasis (Chen et al., 2006). Recent studies have demonstrated that high plasma levels of soluble P-selectin are strongly associated with VTE (Rectenwald et al., 2005). In a prospective cohort study, P-selectin was also shown to be a risk factor for recurrent VTE (Kyrle et al., 2007).

In a recent study, the Vienna Cancer and Thrombosis Study (VCATS) group reported that elevated serum P-selectin levels predicts VTE in 687 newly diagnosed cancer patients. The cumulative probability of VTE after 6 months of follow up was 11.9% in patients with serum P-selectin above and 3.7% in those below the 75th percentile (P = 0.002). Authors postulated that such biomarker could identify cancer patient who may benefit from prophylaxis (Ay et al., 2008).

The concept of VTE prophylaxis for ambulatory cancer patients was tested in a recent double-blind study; patients with metastatic or locally advanced cancer of lung, colo-rectal, stomach, ovary, pancreas, or bladder who are initiating a new chemotherapy course, were randomized to receive subcutaneous semuloparin (a new ultra low molecular weight heparin) or placebo. The drug was given at a dose of 20 mg subcutaneously and continued until change of chemotherapy. Twenty of the 1,608 patients treated with semuloparin (1.2%) and 55 of the 1,604 patients treated with placebo (3.4%) had a thromboembolic event, representing a 64% risk reduction in such event rate (hazard ratio [HR] = 0.36, 95% confidence interval [CI] 0.21–0.60, p<0.0001, intent-to-treat analysis). Nineteen of 1,589 patients (1.2%) in the semuloparin and 18 of the 1,583 patients (1.1%) in the placebo group had a major bleeding (HR=1.05, 95%CI 0.55 to 1.99) (Agnelli et al., 2011).

More work is needed before taking findings of these studies to clinical practice; as such ambulatory cancer patients on active chemotherapy may be considered for VTE prophylaxis based on risk level and clinical judgment.

6. VTE Prophylaxis in cancer patients undergoing surgery

Surgical interventions, both elective and emergency, increase VTE risk in cancer patients compared to similar interventions in non-cancer patients (Gallus, 1997; Kakkar et al., 2005; White et al., 2003;). Despite the utilization of VTE prophylaxis, one multicenter prospective study showed that VTE was the most frequent cause of 30-day mortality in cancer patients undergoing surgical procedures (Agnelli et al., 2006). Though low dose unfractionated heparin (LDUH) is effective in VTE prophylaxis, the drug should be given at the 5000 IU three times a day (not twice) in high risk surgical procedures like pelvic gynecological cancer procedures. LMWH, given once daily, is at least as effective as UFH for this indication (Clark-Pearson et al., 1990).

The issue of extended out-of-hospital prophylaxis in high risk surgical patients was addressed in major clinical trials (Gallus, 1997; Kakkar et al., 2005). In one double-blind, multicenter trial (ENOXACAN II), 322 patients undergoing planned curative open surgery for abdominal or pelvic cancer received enoxaparin (40 mg subcutaneously) daily for 6 to 10 days and were then randomly assigned to receive either enoxaparin (at the same dose) or placebo for another 21 days. Bilateral venography was performed between days 25 and 31, or sooner if symptoms of VTE occurred. In an intention-to-treat analysis and following the double-blind phase, VTE occurred in 4.8% in the extended enoxaparin group compared to 12.0% in the placebo group (P=0.02). This difference persisted at three months (13.8 % vs. 5.5%, P=0.01). There were no significant differences in the rates of bleeding or other complications during the double-blind or follow-up periods (Bergqvist et al., 2002).

In another open-label randomized trial designed to evaluate the efficacy and safety of thromboprophylaxis with dalteparin, another LMWH, administered for 28 days after major abdominal surgery compared to 7 days treatment. A total of 590 patients undergoing major abdominal surgery (60% for cancer) were recruited. The cumulative incidence of VTE was reduced from 16.3% with short-term (7days) thromboprophylaxis to 7.3% after prolonged thromboprophylaxis; a relative risk reduction (RR) of 55%; 95% confidence interval 15-76; P=0.012. The number that needed to be treated to prevent one case of VTE was 12 (95%

confidence interval 7-44). Bleeding events were not increased with prolonged compared with short-term thromboprophylaxis (Rasmussen et al., 2006).

A recent meta-analysis of eligible clinical studies compared safety and efficacy of extended use of LMWH (for three to four weeks after surgery) versus conventional in-hospital prophylaxis among patients undergoing major abdominal surgeries. The indication for surgery was neoplastic disease in 70.6% (780/1104) of patients. The administration of extended LMWH prophylaxis significantly reduced the incidence of VTE, 5.93% versus 13.6%, RR 0.44 (CI 95% 0.28 - 0.7); DVT 5.93% versus 12.9%, RR 0.46 (CI 95% 0.29 - 0.74); proximal DVT 1% versus 4.72%, RR 0.24 (CI 95% 0.09 - 0.67). These superior efficacy results were obtained with no significant difference in major or minor bleeding between the two groups: 3.85% in the extended thrombo-prophylaxis group versus 3.48% in the conventional prophylaxis group; RR 1.12 (CI 95% 0.61 - 2.06) (Bottaro et al., 2008). Given the results of these studies, one can conclude that extended thromboprophylaxis with LMWH should be considered as a safe and useful strategy to prevent VTE in high-risk major abdominal and pelvic surgeries especially in cancer patients. Similar conclusions were reached in a more recent Cochrane database analysis (Rasmussen et al., 2009). Results of these studies are summarized in Figure-1.

7. Central venous catheters

Central venous catheters (CVC) are commonly inserted in cancer patient and are utilized to deliver chemotherapy, blood and blood component transfusion and occasionally for blood sampling. Central catheter per se is a risk factor for VTE, this risk is even higher when such catheters are placed in cancer patients especially so when used for active chemotherapy (Bona, 1999; Rooden et al., 2005; Rosovsky & Kuter, 2005).

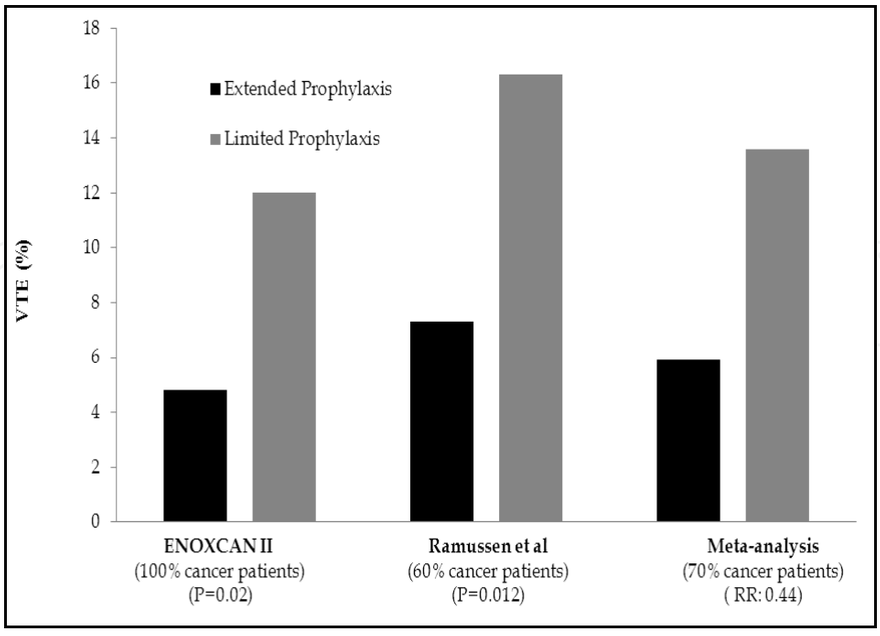

Fig. 1. Extended out-of-hospital VTE prophylaxis for cancer patients undergoing major surgery

Several clinical trials have addressed the issue of VTE prophylaxis in such patients. One study showed a benefit in reducing VTE events when low fixed-dose warfarin (1mg/day) was used for prophylaxis (Bern et al., 1990). However, two subsequent clinical trials failed to show any benefit [Heaton et al., 2002: Couban et al., 2005).

Low molecular weight heparin was also tried in two large, double-blind clinical trials (Verso et al., 2005; Karthaus et al., 2006). The first trial failed to show beneficial effect of enoxaparin when used at a dose of 40 mg once daily versus placebo in a group of 385 cancer patients with CVC (Verso et al., 2005). In the second trial, dalteparin at 5,000 units once daily was tested against placebo in 439 cancer patients who were receiving chemotherapy through such catheters; clinically relevant VTE occurred in 3.7% and 3.4% in the dalteparin and placebo recipients, respectively (Karthaus et al., 2006). Nadroparin, another LMWH, showed no advantage when tested against low fixed dose of warfarin (1 mg/day) in a small randomized trial that involved 45 evaluable patients (Mismetti et al., 2003).

Given the results of these studies, thromboprophylaxis with anticoagulants for patients with central venous catheters is not recommended.

8. Inferior Vena Cava (IVC) filters in cancer patients

Treatment of VTE typically includes initial anticoagulation with unfractionated heparin, LMWH or a pentasaccharide like fondaparinux, (Buller et al., 2004) along with vitamin K antagonists like warfarin. Occasionally, specific clinical situations present in which the risk of PE is very high or systemic anticoagulation might be associated with high risk of bleeding; in these instances, IVC filters are utilized to provide mechanical thromboprophylaxis to prevent PE, the life-threatening complication of VTE. Such filters are inserted using a relatively noninvasive technique to maintain central flow. Thanks to newer technology, the IVC filters are becoming a very attractive option and can function with anticoagulation to optimize the prophylaxis strategy. Inferior Vena Cava filters are usually utilized in many clinical situations detailed in table-2 (Schwarz et al., 1996; Saour et al., 2009).

However, many of such indications are subjective and consensus might occasionally be difficult to reach. In a community-based study, researchers at McMaster University reviewed 1547 local county residents with confirmed diagnosis of acute VTE and without a prior IVC filter. Following the VTE, 203 (13.1%) patients had an IVC filter placed. In reviewing the indications for IVC filter placement, panel members unanimously agreed that the use of IVC filter was appropriate in 51% of the cases and inappropriate in 26%; no consensus was reached in the remaining 23% of the cases (Spencer et al., 2010).

The clinical benefit of IVC filter placement was addressed in one prospective trial (the PREPIC study) in which 400 patients with proximal DVT who were at risk for PE, were randomized to receive IVC filter (200 patients) or no filter (200 patients). Both groups were anticoagulated with LMWH or unfractionated heparin. At day 12, two (1.1%) patients assigned to receive filters, as compared with nine (4.8%) patients assigned to receive no filters, had symptomatic or asymptomatic PE (odds ratio, 0.22; 95 percent confidence interval, 0.05 to 0.90). However, at two years, 37 (20.8%) patients assigned to the filter group,

as compared with 21 (11.6%) patients assigned to the no-filter group, had recurrent DVT (odds ratio, 1.87; 95% CI, 1.10 to 3.20) (Decousus et al., 1998). This study was updated 8 years later; patients with IVC filters experienced a greater cumulative incidence of symptomatic DVT (35.7%versus 27.5%; HR 1.52, CI 1.02 to 2.27; P = 0.042), but significantly fewer symptomatic pulmonary emboli (6.2%versus 15.1%; HR 0.37, CI 0.17 to 0.79; P = 0.008) (The PREPIC Study Group, 2005). The conclusion from this long-term follow-up was similar to the original report; that is, with an IVC filter there is an equivalent trade-off of fewer PE at the cost of more DVTs. There was no difference in long-term morbidity or mortality in both groups.

Main Indications:
Failure of anticoagulation: Recurrent VTE despite anticoagulation
Contraindications and/or severe complications of anticoagulation:
High risk for bleeding
Real bleeding (GI,GU,GYN, CNS)
Thrombocytopenia (Depends on count and etiology)
Immediate post-operative VTE
Large CNS Tumor: Primary or metastatic
Other indications:
Large, free-floating iliocaval thrombus
Limited cardiopulmonary reserve (Cor Pulmonale)
Poor compliance with medications
Patients at risk for falls while on anticoagulation therapy

IVC: Inferior Vena Cava, GI: Gastrointestinal, GU: Genitourinary, GYN: Gynecological, CNS: Central Nervous System, VTE: Venous Thromboembolism

Table 2. Indications for IVC filter placement

Given the lack of long term benefits of IVC filters; temporary, retrievable filters had gained increasing interest. Many different retrievable filters had recently received approval for temporary insertion. Recent data suggest that the use of these filters may be associated with low rates of PE and insertion complications (Imberti & Prisco, 2008). Nevertheless; no randomized clinical trials have been performed. In one large retrospective study that included 252 evaluable patients who had retrievable filter placed for different indications; only 47 filters were successfully retrieved yielding a retrieval rate of 18.7% (Dabbagh et al., 2010). Similar or higher retrieval rates were reported by others (Mismetti et al., 2007).

Regardless of the type of the filter placed, the most recent American Colleague of Chest Physicians (ACCP) guidelines recommend systemic anticoagulation, when possible, even with the filter in place (Kearon et al., 2008).

Cancer itself, or its treatment, might result in certain clinical complications that make systemic anticoagulation very risky (Abdel-Razeq et al., 2011). Venous thromboembolic disease is a frequent complication in patients with intracranial malignancies. Many of the primary brain tumors like gliomas or secondary metastatic tumors to the brain are either bulky or very vascular thus increasing the risk of bleeding with or without systemic anticoagulation (Ruff & Posner, 1983). Brain metastases from melanoma, choriocarcinoma, thyroid carcinoma, and renal cell carcinoma have particularly high propensities for

spontaneous hemorrhage while metastatic tumors from sites like lung and breast are less likely to bleed spontaneously (Mandybur, 1993). However, not all patients with intracranial malignancies are at higher risk of bleeding with anticoagulation. Complication rate of IVC filters in patients with brain tumors is higher than commonly perceived and may outweigh the risk of anticoagulation. Researchers at Brigham and Women's Hospital in Boston reviewed the records of 49 patients with intracranial malignancies and venous thromboembolic disease to determine the effectiveness and complications resulting from systemic anticoagulation or IVC filter placement. Of the 42 patients received IVC filters, a strikingly high percentage (62%) developed one or more complications; 12% developed recurrent PE, while 57% developed filter thrombosis, recurrent DVT, or post-phlebitic syndrome. These complications severely reduced the quality of life of affected patients. Only 15 (31%) patients were treated with anticoagulation, and seven of these received it because of continued thromboembolic disease. None of these 15 patients had proven hemorrhagic complications (Levin et al., 1993).

Many recent studies questioned the need to insert IVC filters in cancer patients particularly those with advanced-stage disease whose survival is short and prevention of PE may be of little clinical benefit and could be a poor utilization of resources. In one retrospective study performed to determine the clinical benefit of IVC filter placement in patients with malignancy, 116 patients who had such filters inserted were included. Ninety one (78%) patients had stage IV disease, 42 (46%) of them died of cancer within 6 weeks and only16 (14%) were alive at one year (Jarrett et al., 2002).

The benefits of IVC filter placement on overall survival, as measured from the time of VTE was addressed in a recent retrospective study that examined 206 consecutive cancer patients with VTE. Patients were classified into 3 treatment groups: anticoagulation-only (n= 62), IVC filter-only (n=77), or combination of both IVC filter and anticoagulation (n=67). Median overall survival was significantly greater in patients treated with anticoagulation (13 months) compared with those treated with IVC filters (2 months) or combination of both (3.25 months; $P < 0.0002$). IVC patients were at 1.9 times more risk of death than anticoagulation only (hazard ratio=0.528; 95% confidence interval=0.374 to .745). Multivariate analysis revealed that performance status and type of thrombus were not confounders and had no effect on overall survival (Barginear et al., 2009).

In another study, the survival benefit of IVC filters in patients with late-stage malignancy was evaluated in a group of 5,970 patients who were treated with a primary diagnosis of malignancy at a tertiary care facility. Retrospective analysis identified 55 consecutive patients with stage III or IV malignant disease and VTE who received IVC filters. In a case control study, 16 patients with VTE but without IVC filter were matched for age, sex, type of malignancy, and stage of disease. Filter placement prevented PE in 52 (94.5%) patients, however, four (7.3%) of patients had complications related to the procedure; 13 (23.6%) patients with late-stage cancer survived less than 30 days following placement of the filter; another 13 (23.6%) patients of this group, however, survived more than one year. Ambulatory status differed significantly ($P = 0.01$) between these two subgroups. Authors concluded that IVC filter placement conferred no survival benefit compared to the control group and that the survival of such patients with advanced-stage cancer was limited

primarily by the malignant process (Schunn et al., 2006). Researchers at M.D. Anderson Cancer center concluded, in a study that included 308 cancer patients with VTE and IVC filters, that such filters are safe and effective in preventing PE-related deaths in selected patients with cancer. However, patients with a history of DVT and bleeding or advanced disease had the lowest survival after IVC filter placement (Wallace et al., 2004).

9. Conclusions and future directions

Despite its proven efficacy, VTE prophylaxis in cancer patients is clearly underutilized. Strategies to improve prophylaxis rate in such high risk patients are highly needed (Abdel-Razeq, 2010). Establishment of "VTE prophylaxis multidisciplinary team" addressing this issue supported by hospital administration might help. Recently, many health advocacy groups and policy makers are paying more attention to VTE prophylaxis. The National Quality Forum (NQF) recently endorsed strict VTE risk assessment evaluation for each patient upon admission and regularly thereafter (National Quality Forum (NQF), 2011). Additionally, the Joint Commission has recently approved new measure sets that included VTE prophylaxis; this standard mandates that a VTE prophylaxis method is in place within 24 hours of hospital admission, otherwise, a risk assessment and contraindications for prophylaxis should be documented for each and every hospitalized medical or surgical patient (The Joint Commission Manual for Performance Improvement Measures, 2011). Recently, Maynard and Stein (2011) have published their experience and recommendations following their extensive efforts to better utilize VTE prophylaxis in high-risk patients. Such recommendations are worth careful attention and are summarized in table-3.

Support by hospital administration for better VTE prophylaxis initiative.
Establishment of VTE Prophylaxis "Multidisciplinary Team"; this team should:
Standardize the process of providing VTE prophylaxis
Facilitates implementation of guidelines.
Audit and monitor outcomes.
Report regularly to hospital administration or a "Quality Council".
Better guidelines:
Simple, yet efficient in daily use; two to three VTE risk levels are enough!
Provide clear link between risk level and prophylaxis choice.
Provide guidance to manage patients with contraindications.
Continuous education and training of all health care providers.

Table 3. Strategies to improve VTE prophylaxis in high risk cancer patients.

In conclusion, though published guidelines are somewhat different; hospitalized cancer patients, in the absence of bleeding or absolute contraindications, should be considered for thromboprophylaxis. Certain cancers, like Multiple Myeloma when treated with drugs like thalidomide or other immune modulators may benefit from prophylaxis. However, current guidelines do not recommend prophylaxis for ambulatory cancer patients or patients with central venous catheter.

Extended thromboprophylaxis with LMWH (21-28days) should be considered in cancer patients undergoing major pelvic/abdominal surgeries.

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11. References

Abdel-Razeq H. (2010). Venous thromboembolism prophylaxis for hospitalized medical patients, current status and strategies to improve. *Ann Thorac Med*. 5:195-200.

Abdel-Razeq, HN.; Hijjawi, SB.; Jallad, SG.; Ababneh, BA. (2010). Venous thromboembolism risk stratification in medically-ill hospitalized cancer patients. A comprehensive cancer center experience. *J Thromb Thrombolysis*. 30: 286-93.

Abdel-Razeq, H.; Mansour, A.; Ismael, Y.; Abdulelah, H. (2011) Inferior vena cava filters in cancer patients: to filter or not to filter. *Ther Clin Risk Manag*. 7:99-102.

Abdel-Razeq, H.; Albadainah, F.; Hijjawi, S.; Mansour, A.; Treish, I. (2011). Venous Thromboembolism (VTE) in Hospitalized Cancer Patients: Prophylaxis Failure or Failure to Prophylax. *J Thromb Thrombolysis*. 3: 107-12.

Ageno, W.; Squizzato, A.; Ambrosini, F. *et al.* (2002). Thrombosis prophylaxis in medical patients: a retrospective review of clinical practice patterns. *Haematologica* 87:746–50.

Agnelli, G.; Bolis, G.; Capussotti, L. *et al.* (2006). A clinical outcome based prospective study on venous thromboembolism after cancer surgery: the ARISTOS project. *Ann Surg* 243:89–95.

Agnelli, G.; George, D.; Fisher, K.; Kakkar, AK. *et al.* (2011). The ultra-low molecular weight heparin (ULMWH) semuloparin for prevention of venous thromboembolism (VTE) in patients with cancer receiving chemotherapy: SAVE ONCO study. *J Clin Oncol 29*: (suppl; abstr LBA9014)

Andtbacka, RH.; Babiera, G.; Singletary, SE. *et al.* (2006). Incidence and prevention of venous thromboembolism in patients undergoing breast cancer surgery and treated according to clinical pathways. *Ann Surg* 243:96–101.

ATAC (Arimidex Tamoxifen Alone or in Combination) Trialists' Group. (2002). Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 359: 2131-2139

Ay, C.; Simanek, R.; Vormittag, R. *et al.* (2008). High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). *Blood* 112:2703–8.

Barginear, MF.; Lesser, M.; Akerman, ML. *et al.* (2009). Need for inferior vena cava filters in cancer patients: a surrogate marker for poor outcome. *Clin Appl Thromb Hemost.* 15:263-269.

Baz, R.; Li, L.; Kottke-Marchant, K. *et al.* (2005). The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc* 80:1568-74.

Belch, JJ.; Lowe, GDO.; Ward, AG.; Forbes, CD.; Prentice, CRM. (1981). Prevention of deep vein thrombosis in medical patients by low-dose heparin. *Scott Med J* 26:115–7.

Bergqvist, D.; Agnelli, G.; Cohen, AT. *et al.* (2002). Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med* 346:975– 80.

Bern, MM.; Lokich, JJ.; Wallach, SR. *et al.* (1990). Very low doses of warfarin can prevent thrombosis in central venous catheters: a randomized prospective trial. *Ann Intern Med* 112,423-8.

Blom, JW.; Doggen, CJ.; Osanto, S.; Rosendaal, FR. (2005). Malignancies, prothrombotic mutations, and risk of venous thrombosis. *JAMA* 293:715–22.

Bohlius, J.; Wilson, J.; Seidenfeld, J. *et al.* (2006). Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst* 98:708–14.

Bona, RD. (1999). Thrombotic complications of central venous catheters in cancer patients. *Semin Thromb Haemost* 25,147-55.

Bottaro, FJ.; Elizondo, MC.; Doti, C. *et al.* (2008). Efficacy of extended thrombo-prophylaxis in major abdominal surgery: what does the evidence show? A meta-analysis. *Thromb Haemost*. 99:1104-11.

Breast International Group (BIG) 1–98 Collaborative Group. (2005). A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 353, 2747-57.

Buller, HR.; Davidson, BL.; Decousus, H. *et al.* (2004). Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med.* 140: 867-873.

Caprini, J.; Arcelus, J.; Reyna, J. (2001). Effective risk stratification of surgical and nonsurgical patients for venous thromboembolic disease. *Semin Hematol* 38:12–19.

Carson, JL.; Kelley, MA.; Duff, A. *et al.* (1992). The clinical course of pulmonary embolism. *N Engl J Med* 326:1240–5.

Cavo, M., Zamagni, E., Tosi, P., *et al.* (2004). First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma. *Haematologica* 89:826-31.

Chen, M., Geng, JG., P-selectin. (2006). mediates adhesion of leukocytes, platelets, and cancer cells in inflammation, thrombosis, and cancer growth and metastasis. *Arch Immunol Ther Exp* 54:75-84.

Chew, HK.; Wun, T.; Harvey, D.; Zhou, H.; White, RH. (2006). Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med* 166:458–64.

Chew, HK.; Wun, T.; Harvey, DJ.; Zhou, H.; White, RH. (2007). Incidence of venous thromboembolism and the impact on survival in breast cancer patients. *J Clin Oncol* 25:70–6.

Chopard, P.; Dörffler-Melly, J.; Hess, U. *et al.* (2005). Venous thromboembolism prophylaxis in acutely ill medical patients: definite need for improvement. *J Intern Med* 257:352–7.

Clark-Pearson, DL.; DeLong, E.; Synan, IS.; Soper, JT.; Creasman, WT.; Coleman, RE. (1990). A controlled trial of two low-dose heparin regimens for the prevention of postoperative deep vein thrombosis. *Obstet Gynecol* 75:684–9.

Couban, S.; Goodyear, M.; Burnell, M. *et al.* (2005). Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. *J Clin Oncol* 23, 4063-9.

Dabbagh, O.; Nagam, N.; Chitima-Matsiga, R.; Bearelly, S.; Bearelly, D. (2010). Retrievable inferior vena cava filters are not getting retrieved: where is the gap? *Thromb Res*. 126:493-497.

Decousus, H.; Leizorovicz, A.; Parent, F. *et al.* (1998). A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis: Prevention duRisque d'Embolie Pulmonaire par Interruption Cave Study Group. *N Engl J Med.* 338:409–415.

Dimopoulos, M.; Spencer, A.; Attal, M. *et al.* (2007). Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 357:2123-32.

Donati, MB. (1995). Cancer and thrombosis: from Phlegmasia alba dolens to transgenic mice. *Thromb Haemost* 74:278.

Fisher, B.; Costantino, JP.; Wickerham, DL. *et al.* (2005). Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 97: 1652-62.

Gallus, AS. (1997). Prevention of post-operative deep leg vein thrombosis in patients with cancer. *Thromb Haemost* 78:126–32.

Geerts, WH.; Bergqvist, D.; Pineo, GF. *et al.* (2008). Prevention of venous thromboembolism: American College of Chest Physicians evidence- based clinical practice guidelines (8th edition). *Chest* 133:381–453.

Gerber, DE.; Grossman, SA.; Streiff, MB. (2006). Management of venous thromboembolism in patients with primary and metastatic brain tumors. *J Clin Oncol* 24:1310–8.

Haddad, TF.; Greeno, EW. (2006). Chemotherapy-induced thrombosis. *Thromb Res* 118:547–666

Heaton, DC.; Han, DY.; Inder, A. (2002). Minidose (1 mg) warfarin as prophylaxis for central vein catheter thrombosis. *Intern Med J* 32: 84-8.

Heit, JA.; Silverstein, MD.; Mohr, DN.; Petterson, TM.; O'Fallon, WM.; Melton, LJ .; 3rd. (2000). Risk factors for deep vein thrombosis and pulmonary embolism: a population based case-control study. *Arch Intern Med* 160:809–15.

Imberti, D.; Prisco, D. (2008). Retrievable vena cava filters: key considerations. T*hromb Res*. 122:442-449.

Jarrett, BP.; Dougherty, MJ.; Calligaro, KD. (2002). Inferior vena cava filters in malignant disease. *J Vasc Surg*. 36:704-707.

Johnson, DH.; Fehrenbacher, L.; Novotny, WF. *et al.* (2004). Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 22:2184-91.

Kabbinavar, F.; Hurwitz, HI.; Fehrenbacher, L. *et al.* (2003). Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 21:60-5.

Kahn, SR.; Panju, A.; Geerts, With. *et al.* (2007). Multicenter evaluation of the use of venous thromboembolism prophylaxis in acutely ill medical patients in Canada. *Thromb Res* 119:145–55.

Kakkar, AK.; Levine, M.; Pinedo, HM.; Wolff, R.; Wong, J. (2003). Venous thrombosis in cancer patients: insights from the FRONTLINE survey. *Oncologist* 8:381-8.

Kakkar, AK.; Haas, S.; Wolf, H.; Encke, A. (2005). Evaluation of perioperative fatal pulmonary embolism and death in cancer surgical patients: the MC-4 cancer substudy. *Thromb Haemost* 94:867–71.

Karthaus, M.; Kretzschmar, A.; Kröning, H. *et al.* (2006). Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. *Ann Oncol* 17: 289-96.

Kearon, C.; Kahn, SR.; Agnelli, G.; Goldhaber, S.; Raskob, GE.; Comerota, AJ. (2008).American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 133(6 Suppl):454S-545S.

Khorana, AA.; Kuderer, NM.; Culakova, E.; Lyman, GH.; Francis, CW. (2008). Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 111:4902–7.

Kniffin, WD.; Baron, JA.; Barret, J.; Bikmeyer, JD.; Anderson, FA. (1994). The epidemiology of pulmonary embolism and deep venous thrombosis in the elderly. *Arch Intern Med* 154:861–6.

Kyrle, PA.; Hron, G.; Eichinger, S.; Wagner, O. (2007). Circulating P-selectin and the risk of recurrent venous thromboembolism. *Thromb Haemost* 97:880-883

Levin, JM.; Schiff, D.; Loeffler, JS.; Fine, HA.; Black, PM.; Wen, PY. (1993). Complications of therapy for venous thromboembolic disease in patients with brain tumors. *Neurology.* 43:1111-1114.

Lyman, GH.; Khorana, AA.; Falanga, A. *et al.* (2007). American Society of Clinical Oncology Guideline: Recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol* 25:5490–5505.

Mandybur, TI. (1977). Intracranial hemorrhage caused by metastatic tumors. *Neurology.* 27:650-655.

Marras, LC.; Geerts, WH.; Perry, JR. (2000). The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. *Cancer* 89:640–6.

Maynard,G.; Stein, J. (2010). Designing and implementing effective venous thromboembolism prevention protocols: Lessons from collaborative efforts. *J Thromb Thrombolysis* 29:159-66

Minnema, MC.; Breitkreutz, I.; Auwerda, JJ. *et al.* (2004). Prevention of venous thromboembolism with low molecular-weight heparin in patients with multiple myeloma treated with thalidomide and chemotherapy. *Leukemia* 18:2044-6.

Mismetti, P.; Mille, D.; Laporte, S. *et al.* (2003). Low-molecular-weight heparin (nadroparin) and very low doses of warfarin in the prevention of upper

extremity thrombosis in cancer patients with indwelling long-term central venous catheters: a pilot randomized trial. *Haematologica* 88,67-73.

Mismetti, P.; Rivron-Guillot, K.; Quenet, S. *et al.* (2007). A prospective long-term study of 220 patients with a retrievable vena cava filter for secondary prevention of venous thromboembolism. *Chest*. 131:223-229.

Monreal, M.; Kakkar, AK.; Caprini, JA. *et al.* (2004). The outcome after treatment of venous thromboembolism is different in surgical and acutely ill medical patients. Findings from the RIETE registry. *J Thromb Haemost* 2:1889–91.

Motykie, G.; Zebala, L.; Caprini, J. *et al.* (2000). A guide to venous thromboembolism risk factor assessment. *J Thromb Thrombolysis* 9:253–62.

National Quality Forum (NQF) . (2011). at (NQF). Available from: http://www.qualityforum.org/Measures_List.aspx#k=THROMBOSIS [last cited on Apr 06, 2011].

Palumbo, A.; Cavo, M.; Bringhen, S. *et al.* (2011). Aspirin, Warfarin, or Enoxaparin Thromboprophylaxis in Patients with Multiple Myeloma Treated With Thalidomide: A Phase III, Open-Label, Randomized Trial. *J Clin Oncol* 29:986-993.

Pengo, V.; Lensing, AW.; Prins, MH. *et al.* (2004). Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 350:2257–64.

Prandoni, P.; Lensing, AWA.; Buller, HR. *et al.* (1992). Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. *N Engl J Med* 327:1128-33

Prandoni, P.; Lensing, AW.; Cogo, A. *et al.* (1996). The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 125:1–7.

Pritchard, KI.; Paterson, AH.; Paul, NA.; Zee, B.; Fine, S.; Pater, J. (1996). Increased thromboembolic complications with concurrent tamoxifen and chemotherapy in a randomized trial of adjuvant therapy for women with metastatic breast cancer. *J Clin Oncol* 14: 2731-7.

Rasmussen, MS.; Jorgensen, LN.; Wille-Jørgensen, P. *et al.* (2006). Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. *J Thromb Haemost* 4:2384–90.

Rasmussen, MS.; Jørgensen, LN.; Wille-Jørgensen, P. (2009). Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. *Cochrane Database Syst Rev*. 1):CD004318.

Rectenwald, JE.; Myers, DD Jr.; Hawley, AE. *et al. (2005).* D-dimer, P-selectin, and microparticles: novel markers to predict deep venous thrombosis. A pilot study. *Thromb Haemost* 94:1312-1317

Rooden, CJ.; Tesselaar, ME.; Osanto, S.; Rosendaal, FR.; Huisman, MV. (2005). Deep vein thrombosis associated with central venous catheters: a review. *J Thromb Haemost* 3: 2409-19.

Rosovsky, RP.; Kuter, DJ. (2005). Catheter-related thrombosis in cancer patients: pathophysiology, diagnosis, and management. *Hematol Oncol Clin N Am* 19: 183-202.

Ruff, RL.; Posner, JB. (1983). The incidence and treatment of peripheral venous thrombosis in patients with glioma. *Ann Neurol.* 13:334-336.

Sallah. S.; Wan, JY.; Nguyen, NP. (2002). Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. *Thromb Haemost* 87:575–9.

Saour, J.; Al Harthi, A.; El Sherif, M.; Bakhsh, E.; Mammo, L. (2009). Inferior vena caval filters: 5 years of experience in a tertiary care center. *Ann Saudi Med.* 29:446-449.

Schunn, C.; Schunn, GB.; Hobbs, G.; Vona-Davis, LC.; Waheed ,U. (2006). Inferior vena cava filter placement in late-stage cancer. *Vasc Endovascular Surg.* 40:287-294.

Schwarz, RE.; Marrero, AM.; Conlon, KC.; Burt, M. (1996). Inferior vena cava filters in cancer patients: indications and outcome. *J Clin Oncol.* 14:652-657.

Shah, MA.; Ilson, D.; Kelsen, DP. (2005). Thromboembolic events in gastric cancer: High incidence in patients receiving irinotecan- and bevacizumabbased therapy. *J Clin Oncol* 23:2574-6.

Sørensen, HT.; Mellemkjaer, L.; Olsen, JH.; Baron, JA. (2000). Prognosis of cancers associated with venous thromboembolism. *N Engl J Med* 343:1846–50.

Spencer, FA.; Bates, SM.; Goldberg, RJ. *et al.* (2010). A population-based study of inferior vena cava filters in patients with acute venous thromboembolism. *Arch Intern Med.* 170:1456-1462.

Tapson, VF.; Decousus, H.; Pini, M. *et al.* (2007). Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the international medical prevention registry on venous thromboembolism. *Chest* 132:936–45.

The Joint Commission Manual for Performance Improvement Measures. (2011). Available from: http://www.jointcommission.org/venous_thromboembolism/ [last cited on, Apr 06, 2011].

The PREPIC Study Group. (2005). Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Pre´vention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. *Circulation.* 112:416–422.

Thodiyil, PA.; Kakkar, AK. (2002). Variation in relative risk of venous thromboembolism in different cancers. *Thromb Haemost* 87:1076–7.

Verso, M.; Agnelli, G.; Bertoglio, S. et al. (2005). Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. *J Clin Oncol* 23, 4057-62.

Wagman, LD.; Baird, MF.; Bennett, CL. *et al.* (2008). Venous thromboembolic disease. NCCN. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 6:716–53.

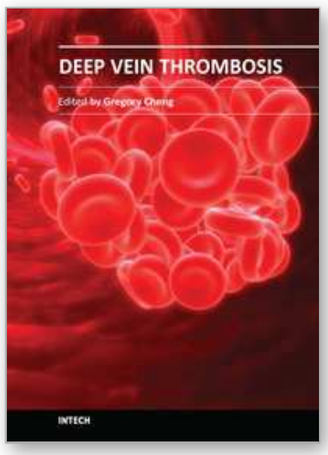
Wallace, MJ.; Jean, JL.; Gupta, S. *et al.* (2004). Use of inferior vena caval filters and survival in patients with malignancy. *Cancer.* 101:1902-1907.

White, RH.; Zhou, H.; Romano, PS. (2003). Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost* 90:446–55.

Zangari, M.; Siegel, E.; Barlogie, B. *et al.* (2002). Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. *Blood* 100:1168-71.

Zangari, M.; Fink, LM.; Elice, F.; Zhan, F.; Adcock, DM.; Tricot, GJ. (2009). Thrombotic events in patients with cancer receiving antiangiogenesis agents. *J Clin Oncol* 27: 4865-73

Zonder, JA.; Barlogie, B.; Durie, BG.; McCoy, J.; Crowley, J.; Hussein, MA. (2006). Thrombotic complications in patients with newly diagnosed multiple myeloma treated with lenalidomide and dexamethasone: Benefit of aspirin prophylaxis. *Blood* 108:403.



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This book provides a comprehensive review of deep vein thrombosis. There are chapters on risk factors for DVT, post thrombotic syndrome and its management, vena cava malformation as a new etiological factor and thrombosis in the upper limbs. DVT is usually seen in patients undergoing major surgeries. The guidelines for thrombo-prophylaxis in orthopaedic patients, radical pelvic surgeries, laparoscopic operations and risks versus benefits in regions with a low prevalence of DVT are thoroughly addressed. Cancer and its treatment are recognized risk factors for VTE and extended prophylaxis in ambulatory cancer patients is reviewed. The role of imaging and endovascular therapies in acute DVT, hypercoagulabilty in liver diseases and the challenges in developing countries are discussed.

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