Prevention of Venous ThromboEmbolism in Patients with Cancer

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Abstract

**Background:** Prevention of venous thromboembolism (VTE) in cancer patients remains controversial in most of clinical settings. **Purpose:** The Italian Society for Haemostasis and Thrombosis (SISET) commissioned a project to develop clinical practice guidelines for the prevention of VTE in patients with malignancy. **Methods:** Key questions about prevention of VTE in patient with malignancy were formulated by a multidisciplinary working group consisting of experts in clinical medicine and research. After a systematic review and discussion of the literature, recommendations were formulated and graded according to the supporting evidence. For those questions for which the literature search did not find any definitive answer (absence of evidence, evidence of low quality and/or in contradiction), a formal consensus method was used to issue clinical recommendations anyway. **Results:** Searching on VTE prevention furnished 1021 citations; 69 articles were selected and 24 were used for drafting clinical recommendations. Four areas reached evidence grading A to C: 1) Need of prevention (pharmacological and/or mechanical) in cancer patients undergoing major abdominal or pelvic surgery and in 2) those with an acute medical disease requiring hospitalization and bedridden. Avoid prevention in 3) cancer patients with central venous catheter and 4) those on chemo-radio or hormonal therapy except patients with multiple myeloma treated with thalidomide plus high-dose dexametasone. Six areas were considered clinically important but without evidence from literature thus requiring formal consensus (grade D): 1) need of prevention during chemo-radio or hormonal therapy in patients with previous VTE, 2) optimal duration of pharmacological prevention in patients with hospitalization for acute medical illness and bedridden, 3) optimal duration of pharmacological prevention in patients undergoing major surgery different from abdominal and pelvic, 4) optimal duration of pharmacological prevention in myeloma patients on thalidomide plus dexametasone, 5) presence of cerebral metastasis as contraindication to pharmacological prevention, 6) prevention in cancer patients undergoing surgery by laparoscopic procedures lasting > 30 min. **Conclusion:** Results of the
systematic literature review and an explicit approach to consensus techniques have been written thus producing recommendations for the most clinically important issues in the prevention of VTE in cancer patients
**Introduction**

Venous thromboembolism (VTE) occurs in 4% to 20% of patients, and is one of the leading causes of death in patients with cancer [1, 2]. Cancer cells can promote the activation of blood coagulation directly by generating thrombin, or indirectly by stimulating endothelial cells and circulating mononuclear cells to synthesise and express several procoagulant factors [3-5].

The risk of thrombosis differs across various cancer subgroups and over the natural history of the disease. The risk of VTE is highest in the initial period after the diagnosis of malignancy [6] but this varies according to the type of malignancy and its disease stage. Such risk is also high even in patients who may suffer from thrombocytopenia; in fact, recent studies suggest a strong association with hematologic malignancies, particularly lymphomas [6, 7].

Hospitalized patients with cancer and those receiving active therapy seem to be at the greatest risk for development of VTE as well as those receiving surgical cancer treatments [8]. Cancer chemotherapy has been shown to both amplify the prothrombotic effect of cancer cells and to damage vessel walls directly, and is increasingly recognised as a risk factor for thromboembolic complications [9]. Patients with cancer undergoing surgery have a two-fold increased risk of postoperative Deep Vein Thrombosis (DVT) and a three-fold greater risk of fatal Pulmonary Embolism (PE) compared with patients who do not have cancer having similar surgery [10]. Results from numerous studies have identified the presence of a Central Venous Catheter (CVC) as a risk factor for development of an upper-extremity DVT [11], although discrepancies exist concerning the incidence of CVC-related DVT and the efficacy of pharmacological prophylaxis [12].

Unfortunately, the efficacy and safety of the various prophylaxis methods in these categories as well as the need for prophylaxis in particular settings of patients are not supported by adequate evidence in different contexts, and there are considerable differences in approach in clinical practice.
Therefore, the Italian Society for Haemostasis and Thrombosis (SISET) commissioned a project to develop clinical practice guidelines for the therapy of VTE in patients with malignancies. The recommendations were generated through a systematic search of evidence and formulated according with explicit methods for consensus development.

The objective of the present guidelines was to provide recommendations for the prevention of VTE in cancer patients with particular attention to the topic of chemotherapy-associated thrombosis and areas of uncertain.

**Design and Methods**

*Methods*

These guidelines were issued following a methodology previously defined by the SISET Guidelines Program Steering Group and approved by the SISET Executive Committee. Details on the methodology have been published [13]. The first search of evidence was performed in December 2005, but updated literature searches were continued until December 2010. The grading system adopted is the one designed by the Scottish Intercollegiate Guideline Network (SIGN) [14]. The draft recommendations were reviewed by an external panel of two internationally recognized experts in the field and by SISET Executive Committee.

*Panel composition*

SISET Executive Committee convened a multidisciplinary working group consisting of experts in clinical medicine and research relevant to the treatment of VTE in patients with cancer, including medical and surgical oncologists.

The executive committee of SISET charged one chairman (SS) with the development of the present guidelines, and invited an expert panel made of 9 members of the society selected for their expertise in research and clinical practice in the prevention of VTE (UA, MC, AF, DI, ACM, DP,
MS, MV, AV), 1 expert oncologist (FF) and 1 medical practitioner (RL). The panel members are
listed in Appendix 1.

The present guidelines focus on adult patients with active solid and haematological cancer,
requiring chemo-radio- or surgical therapy or any other approach potentially increasing the risk for
VTE (such as bedridden, implementation of CVC, etc). Literature search was performed using the
MEDLINE (1966 to 2010) and EMBASE (1980 to 2010) electronic databases. For each topic, two
reviewers performed study selection independently, with disagreements resolved through discussion
and by the opinion of a third reviewer, if necessary. Detailed information on search strategies and
results are available upon request. Selected articles were ranked according to a hierarchy of
evidence levels, including systematic reviews, controlled clinical trials, uncontrolled clinical trials
and case series. In the absence of evidence, a formal consensus method was applied. A detailed
description of the organization and methodology of the SISET guidelines is reported elsewhere
[13].

Results

Searching on VTE prevention furnished 1021 citations; 69 articles were selected and 24 were
used for drafting clinical recommendations.

Recommendations

1. Hospitalised patients with malignancies and concomitant acute medical illness should
   receive prophylactic doses of LMWH or Fondaparinux (grade A)

2. In those at high-risk for bleeding or others contraindications to pharmacological
   prophylaxis, mechanical prophylaxis with intermittent leg compression or graduated
   stocking should be implemented (grade C)

3. In patients undergoing surgery for cancer, pharmacological prophylaxis with UFH,
   LMWH, Fondaparinux or Dextran should be given for at least 7 days (grade A)
4. In patients undergoing surgery for cancer, pharmacological prophylaxis may be associated to mechanical prophylaxis (grade C)

5. In surgical cancer patients, pharmacological prophylaxis with Unfractionated (UFH) or LMW Heparin should be commenced preoperatively (grade C)

6. In surgical cancer patients with major abdominal or pelvic surgery, pharmacological prophylaxis with Heparin or Fondaparinux should be continued for 4 weeks (grade A)

7. In cancer patients with CVC, routine prophylaxis is not indicated (grade A)

8. Mechanical prophylaxis is indicated in patients with an increased risk for bleeding (grade C)

9. Pharmacological prophylaxis is not routinely recommended in patients undergoing chemo or radio or hormonal therapy (grade C) except:
   - patients with lung or gastrointestinal cancer should receive Nadroparin (3.800 U anti-FXa daily) for no more than 4 months (grade A)
   - patients with multiple myeloma treated with Thalidomide or Lenalidomide plus High-Dose Dexamethasone should receive LMWH or Aspirin or Warfarin (Grade C)

**Areas of uncertain**

Some areas of uncertain have been discussed among experts who defined the grade of consensus:

1. Patients with previous VTE candidate to chemo-, radio or hormonal therapy, antithrombotic prophylaxis is appropriate (grade D)

2. In cancer patients with concomitant acute medical illness pharmacological prophylaxis up to 4 weeks is uncertain (grade D)

3. In surgical cancer patients without abdominal or pelvic surgery pharmacological prophylaxis up to 4 weeks is appropriate (grade D)
4. In patients receiving Thalidomide/Lenalidomide plus High Dose Dexamethasone, pharmacological prophylaxis up to 6 months is appropriate (grade D).

5. In patients with cerebral localisation of cancer, pharmacological prophylaxis (when needed) is appropriate (grade D).

6. Pharmacological or mechanical prophylaxis is appropriate in cancer patients undergoing laparoscopic procedures lasting > 30 min. (Grade D)

**Literature review and analysis**

**Hospitalized patients**

The reported frequency of VTE in hospitalized patients with cancer ranges from 0.6% to 18% [7, 8]. Patients at particularly high risk for VTE include older patients, patients with cancers of the brain, pancreas, ovary, kidney, bladder, lung, GI tract, hematologic malignancies, patients with metastatic disease, those immobilized, neutropenic and infected. The risk of VTE increases significantly when patients with cancer are hospitalized [8].

Unfortunately, data regarding the efficacy of primary prophylaxis for reducing VTE in this setting of cancer patients are lacking since most of the information comes from non cancer population [15-19]. Three randomized multicenter studies of pharmacologic prophylaxis with either LMWH or fondaparinux in acutely ill hospitalized patients have been reported [15-17]. In all studies patients with cancer constituted only a minority of the population and only one provided outcome data for the cancer subset. Previous studies on medical prophylaxis using UFH (5,000 IU given twice daily) in acutely ill medical patients failed to demonstrate a significant reduction in fatal PE [19] while in other studies, UFH given three times daily (5,000 IU) reached the same efficacy of LMWH [20]. Recent guidelines on VTE prevention in cancer patients (ACCP
guidelines, NCCN, ASCO, AIOM) strongly recommend (1A) pharmacologic prophylaxis with either low-dose UFH or LMWH for bedridden patients with active cancer but these recommendations are based on clinical trials in which only a minority of patients had cancer [21-25]. However, the low complication rates observed with prophylaxis in the major medical trials appear to justify the use of pharmacologic prophylaxis in hospitalized patients with cancer, even if compliance with thromboprophylaxis is low [25].

**Surgical Patients**

The presence of malignant disease doubles the risk for DVT [26] with reported incidences of asymptomatic calf vein thrombi at 40% to 80%, proximal-vein thrombi 10% to 20%, PE 4% to 10%, and fatal PE 1% to 5% without perioperative thromboprophylaxis. The only factor influencing the risk of VTE, other than those found in non cancer patients (age = OR 2.6; duration of anesthesia OR = 4.5; prolonged postoperative immobilization= OR 4.4, and history of a previous episode of VTE = OR6.0), is advanced stage of disease (OR 2.7). All patients undergoing major surgical interventions for malignant disease (laparotomy, laparoscopy, or thoracotomy lasting greater than 30 minutes) are considered at high risk for the development of VTE; thrombo-prophylaxis in the surgical setting includes pharmacologic and mechanical methods [27]. Pharmacologic methods of thromboprophylaxis include UFH, LMWHs, fondaparinux (an indirect inhibitor of activated factor Xa), and the vitamin K antagonists. Potential advantages favouring LMWHs over UFH in cancer surgery prophylaxis include once-daily versus t.i.d. injections and a lower risk of heparin-induced thrombocytopenia [27]. Fondaparinux was found to be at least as effective as dalteparin in preventing VTE in a RCT of high-risk abdominal surgery patients (68% of the entire study population had cancer). A post-hoc analysis suggested improved efficacy in reducing VTE for fondaparinux versus dalteparin in this large subgroup of patients with cancer [28].

Two recent randomized studies suggest that prolonging the duration of prophylaxis up to 4 weeks is even more effective than a shorter duration therapy in reducing postoperative VTE [29,
In a RCT, VTE rates were 4.8% in patients receiving enoxaparin for 4 weeks after surgery for abdominal or pelvic cancer versus 12% in patients receiving enoxaparin for 1 week after surgery (p < 0.02) [29]. In a second randomized study, patients undergoing major abdominal surgery were randomly assigned to receive 4 weeks versus 1 week of dalteparin prophylaxis. VTE rates were 16.3% in the 1-week arm compared with 7.3% in the 4-week prophylaxis arm (p < 0.012) [30]. More than half of patients in each arm in this second study underwent cancer surgery. There was no increase in bleeding complications associated with prolonged prophylaxis in either study.

Regarding specific settings, there are limited data on the benefit of thromboprophylaxis in patients undergoing laparoscopic surgery and none in cancer population. In a large retrospective study in patients with prostate cancer undergoing laparoscopic radical prostatectomy, the rate of symptomatic VTE was low (0.5%) [31]. In the absence of prospective data, however, standard prophylactic regimens may be tailored to individual patient risk factors.

Mechanical methods overcome venous stasis either passively with graduated compression stockings, or actively with intermittent pneumatic calf compression (IPC) or mechanical foot pumps. Recent pooled analyses of studies of all three mechanical methods of thromboprophylaxis, evaluated in different patient populations, indicate that these methods employed as monotherapy for VTE prevention reduce the frequency of DVT by 66%, but only achieve a modest and insignificant reduction of 31% in the frequency of PE [32]. A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients. A Cochrane review of 19 studies showed that low-dose UFH combined with graduated compression stockings was four times more effective for VTE prevention than low-dose UFH alone [33].

*Chemotherapy-associated thrombosis*
There are few data available on the prevention of VTE in outpatients with cancer during chemotherapy.

In one study, Levine et al showed that low-dose warfarin is effective in reducing the rate of thrombosis during chemotherapy. In a double-blind randomized trial, 311 patients with metastatic breast cancer were given either very low dose warfarin (1 mg for 6 weeks followed by adjusted dose to a target INR of 1.3 to 1.9) or placebo while receiving chemotherapy. The rate of thrombosis was 0.65% in the warfarin arm and 4.4% in the placebo arm, a statistically significant 85% risk reduction in the rate of VTE with no increase in bleeding [34].

European investigators presented data in abstract form from two double-blind, placebo-controlled, RCTs (TOPIC-1 and TOPIC-2) in patients with metastatic breast cancer (n. 353) or stage III or IV non–small-cell lung carcinoma (n. 547). Patients were randomly assigned to receive either 6 months of the LMWH certoparin (3,000 anti-factor Xa units daily) or placebo for primary prevention of chemotherapy-associated VTE. In patients with breast cancer, there was no observed difference in the rates of VTE (4%), whereas rates of major bleeding complications during 6 months of treatment were 1.7% for the LMWH arm and 0% for the placebo arm. In patients with lung cancer, there was a non significant trend toward effectiveness of LMWH prophylaxis, with VTE rates of 4.5% for the LMWH arm and 8.3% for the placebo arm (p 0.07). Major bleeding in patients with lung cancer occurred in 3.7% of the LMWH treated patients versus 2.2% in the placebo group. In a post-hoc analysis, rates of VTE in patients with stage IV lung cancer who received LMWH were 3.5% compared with 10.1% for those receiving placebo (p 0.03) [35].

The risk of VTE in patients receiving thalidomide for Multiple Myeloma (MM) has been found to range from 17% to 26% in combination with dexamethasone [36, 37] and from 12% to 28% in combination with other chemotherapy agents including anthracyclines [38, 39]. Recent prospective studies of thalidomide-containing regimens in patients with MM have suggested efficacy for prophylactic anticoagulation with LMWH, warfarin at low fixed doses and aspirin [38-
Palumbo et al evaluated the safety and the efficacy of LMWH or low-dose aspirin (ASA) or low-fixed dose warfarin (WAR) as anticoagulant prophylaxis in a sub study of 991 newly diagnosed MM patients [42]. End-points were incidence of VTE, acute cardiovascular events, sudden death, major and minor bleeding. As anti-myeloma therapy, patients were randomized to VTD (Velcade 1.3 mg/m² d 1,4,8,11; Thalidomide 200 mg/d; Dexamethasone 320 mg/21 d) or TD (Thalidomide 200 mg/d; Dexamethasone 320 mg/21 d) or VMPT (Velcade 1.3 mg/m² d 1,8,15,22; Melphalan 9 mg/m² d 1-4; Prednisone 60 mg/m² d 1-4; Thalidomide 50 mg/d) or VMP (Velcade 1.3 mg/m² d 1,8,15,22; Melphalan 9 mg/m² d 1-4; Prednisone 60 mg/m² d 1-4). In a sub-study, patients treated with VTD or TD or VMPT were randomly assigned to receive LMWH (Enoxaparin 40 mg/d, N=223) or ASA (Aspirin 100 mg/d, N=227) or oral anticoagulants (OAT, Warfarin 1.25 mg/d, N=223) for the duration of the induction therapy; 61 patients were excluded from sub-study because of indication for anticoagulant/antiplatelet therapy or high-risk of bleeding. Patients treated with VMP (N=257) did not receive any prophylaxis and were used as controls. The incidence of VTE was 5% in the LMWH group, 6% in the ASA group and 8% in the OAT group (p not significant). VTEs were 2% in the VMP group. Median time to onset of VTE for patients who received LMWH or ASA or OAT were 4.7, 2.4 and 2.4 months, respectively. Patients who received higher doses of both steroids and thalidomide (VTD and TD) had a higher VTE incidence (7%) in comparison with those who received lower doses (VMPT, 3%, p=0.06). Patients treated with bortezomib (VTD and VMPT) had a lower VTE incidence (5%) in comparison with patients on TD (8%, p=0.08). The rates of cardiovascular events were 2% in the LMWH group, 1% in the ASA group and 0.5% in the OAT group. The incidence of major and minor bleeding was 2% in the LMWH group, 3% in the ASA group and 1% in the WAR group (p not significant). The incidence of combined thrombosis, bleeding and cardiovascular events was 9% in the LMWH group, 10% in the ASA group and 9% in the OAT group (p not significant). Rajkumar et al. reported the results of a phase II trial of lenalidomide (an analog of thalidomide) plus dexamethasone in 34 patients with myeloma [44]. Patients received either 80 or 325 mg of aspirin daily. Although the observed rate of VTE was
lower than in a previous study of lenalidomide plus dexamethasone without aspirin prophylaxis, another trial casts doubt on the efficacy of aspirin as an antithrombotic agent in this population. Cavallo F et al, in patients newly diagnosed with MM, recently presented data on a sub study evaluating the efficacy of LMWH or low-dose aspirin (ASA) as antithrombotic prophylaxis during treatment with lenalidomide and low-dose dexamethasone (Rd) as induction and subsequently randomized to receive consolidation with lenalidomide plus melphalan plus prednisone (MPR) or high dose melphalan (MEL 200) [45]. End-points were incidence of VTE, acute cardiovascular events, sudden death, major and minor bleeding. 402 newly diagnosed MM patients were enrolled in the randomized trial. Treatment schedule included four 28 day cycles of lenalidomide (25 mg days 1–21) and low-dose dexamethasone (40 mg days 1, 8, 15, 22) (Rd) as induction. As consolidation, patients were randomized to receive six 28-day cycles of melphalan (0.18 mg/kg days 1–4), prednisone (2 mg/kg days 1–4) and lenalidomide (10 mg days 1–21) (MPR, N=202) or tandem melphalan 200 mg/m² with stem-cell support (MEL 200, N=200). All eligible patients were randomly assigned to receive LMWH (Enoxaparin 40 mg/d, N=166) or ASA (Aspirin 100 mg/d, N=176) for the duration of the induction therapy and for consolidation therapy in the MPR group; 60 patients were excluded from this sub-study because of indication for anticoagulant/antiplatelet therapy or high-risk of bleeding. During the induction phase, the overall incidence of any grade 3–4 thrombotic events was 1% in the LMWH group, 2.4% in the ASA group (p=.45). VTE, mostly of the lower limbs were equally distributed in the two groups (1%; p not significant), while pulmonary embolism was observed only in the ASA group (2%; p not significant). Median time to onset of thrombotic events for patients who received LMWH or ASA was 2.1 and 1 months, respectively. No acute cardiovascular events were observed and only minor bleeding was detected in the LMWH group (1%). During consolidation no thrombotic events were observed in the MPR group, only one central venous catheter thrombosis was observed in the MEL 200 group.

Agnelli G et al. evaluated ambulatory patients with lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer who were randomly assigned in a double-blind manner to receive
subcutaneous injections of nadroparin (3800 IU anti-Xa once a day, n=779) or placebo (n=387) [46]. Study treatment was given for the duration of chemotherapy up to a maximum of 4 months. The primary study outcome was the composite of symptomatic venous or arterial thromboembolic events, as assessed by an independent adjudication committee. All randomised patients who received at least one dose of study treatment were included in the efficacy and safety analyses (modified intention-to-treat population). A total of 1150 patients were included in the primary efficacy and safety analyses: 769 patients in the nadroparin group and 381 patients in the placebo group. 15 (2.0%) of 769 patients treated with nadroparin and 15 (3.9%) of 381 patients treated with placebo had a thromboembolic event (single-sided p=0.02). Five (0.7%) of 769 patients in the nadroparin group and no patient in the placebo group had a major bleeding event (two-sided p=0.18). The incidences of minor bleeding were 7.4% (57 of 769) with nadroparin and 7.9% (30 of 381) with placebo. There were 121 (15.7%) serious adverse events in the nadroparin group and 67 (17.6%) serious adverse events in the placebo group.

**CVC associated-thrombosis**

The presence of a central venous catheter (CVC) in cancer patients predisposes to upper-extremity DVT [47-51]. In a recent meta-analysis, nine RCTs were evaluated [52]. None of these RCTs tested fondaparinux. The use of heparin in cancer patients with CVC was associated with a trend towards a reduction in symptomatic DVT (Relative Risk (RR) = 0.43; 95% Confidence Interval (CI): 0.18 to 1.06), but the data did not show any statistically significant effect on mortality (RR = 0.74; 95% CI: 0.40 to 1.36), infection (RR = 0.91; 95% CI: 0.36 to 2.28), major bleeding (RR = 0.68; 95% CI: 0.10 to 4.78) or thrombocytopenia (RR = 0.85; 95% CI: 0.49 to 1.46). The effect of warfarin on symptomatic DVT was not statistically significant (RR = 0.62; 95% CI: 0.30 to 1.27). When studies assessing different types of anticoagulants were pooled, symptomatic DVT rates were significantly reduced (RR = 0.56; 95% CI: 0.34 to 0.92) [53]. Although this area remains controversial, prophylactic doses of LMWH cannot be recommended as thromboprophylaxis for cancer patients.
with indwelling CVCs except than in particular situations (such as previous thrombosis or known additional individual risk factors) [53, 54].

Discussion

Patients with cancer represent a high-risk population for VTE although its prevention remains a challenge in terms of both treatment-associated toxicities and scarce available evidence. Notwithstanding these limits, in the last years at least 3 guidelines have been published addressing VTE prevention in cancer patients. The ACCP guidelines on antithrombotic and thrombolytic therapy included chapters on the prevention and treatment of VTE [21-25] but they did not focus specifically on the cancer patient, even if selected issues related to patients with cancer were discussed. The National Comprehensive Cancer Network (NCCN) VTE Panel was convened in 2005 and its more recent guidelines have been published in 2008 [21]. All aspects of VTE (prophylaxis, treatment and related-complications) were discussed and presented in flow-charts; some issues, however, were not discussed but left to further evidence from clinical trials (such as VTE prophylaxis in patients with prolonged thrombocytopenia, VTE prophylaxis in patients with history of CVC related DVT, extended VTE prophylaxis in medical oncology patients). The Italian Association of Medical Oncology (AIOM) has published recommendations to direct the clinical practice in the management of VTE in patients with cancer [23]. These recommendations are comprehensive and focus on six different aspects, including VTE associated with occult cancer, prophylaxis of VTE in cancer surgery, prophylaxis of VTE during chemotherapy or hormonal therapy, prophylaxis of VTE associated with central venous catheters, treatment of VTE in patients with cancer, and anticoagulation and prognosis of cancer. A recent update of AIOM guidelines has been published but only few recommendations regards VTE prophylaxis [22, 23].

Our guideline offers explicit recommendations for the use of anticoagulation and other measures for the prevention of VTE in hospitalized patients with cancer and those receiving cancer
chemotherapy on an ambulatory basis, patients with cancer in the perioperative and postoperative period, those with recent VTE. We also discussed and gave recommendations on areas of uncertainty that meet clinically important issues, such as patients with previous VTE candidate to chemo-, radio or hormonal therapy, duration of VTE prophylaxis in medical cancer patients, subgroups of cancer patients candidate to low-risk surgical approaches, or those with cerebral localisation of cancer who need of pharmacological antithrombotic prophylaxis. Nevertheless, the available data addressing these and related issues are limited and still remains the need for additional research, particularly in the form of large, well designed, randomized, controlled clinical trials.

In conclusion, hospitalized patients with cancer should be considered candidates for VTE prophylaxis in the absence of specific contraindications such as active bleeding even if the recommendations for VTE prophylaxis is based on clinical trials that enrolled, in most cases, only a small proportion of patients with cancer. There are few data available on the prevention of VTE in outpatients with cancer. Additional studies are needed to further evaluate the potential risk of VTE and the value of primary prophylaxis in patients receiving novel targeted therapies, particularly the class of antiangiogenic agents.

Regarding major surgical intervention for malignant disease, all patients should be considered for thromboprophylaxis for at least 7 days postoperatively; prolonged prophylaxis for up to 4 weeks may be considered in high-risk patients even if additional studies are needed to better define the risk-benefit profile of prolonged anticoagulation.
References


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http://www.sign.ac.uk


Appendix 1

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