Review Article

Venous Thromboembolism in Cancer Patients Undergoing Major Abdominal Surgery: Prevention and Management

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Cancer is an important risk factor for venous thrombosis. Venous thromboembolism is one of the most common complications of cancer and the second leading cause of death in these patients. Recent research has given insight into mechanism and various risk factors in cancer patients which predispose to thromboembolism. The purpose of this review is to summarize the current knowledge on the prophylaxis, diagnosis, and management of venous thromboembolism in these patients.

1. Introduction

Professor Armand Trousseau was the first to write about the association between cancer and thrombosis in 1865, and the combination of the two conditions is still often called Trousseau's syndrome [1]. Cancer is an important risk factor for arterial and, more commonly, venous thromboembolism (VTE), which is a spectrum of disease that includes deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE in cancer has an increased incidence due to presence of large number of associated risk factors. Prevention and management of VTE are more challenging in cancer patients in view of the unique pathogenesis, increased rate of complications, and recurrent VTE.

Of all the etiological and predisposing factors, cancer alone was associated with a 4.1-fold risk of thrombosis, and this risk increases to 6.5 fold in cancer patients on chemotherapy [2, 3]. Recent studies have reported an overall sevenfold increase in risk of VTE in cancer patients, with the exact risk varying depending on the primary site of cancer—1.6 fold in head and neck cancers and 28 fold in hematological cancers [4, 5].

Cancer patients undergoing surgery have twice the risk of postoperative VTE and nonfatal pulmonary embolism (PE) and three times the risk of fatal PE, compared to patients undergoing surgery for benign disease, despite the use of thromboprophylaxis [6–8]. In the RISTOS project, a web-based prospective registry, 2372 patients undergoing general, urologic, or gynecologic surgery for cancer were evaluated [9]. Of these, 82% had received in-hospital VTE prophylaxis, yet the incidence of clinically overt VTE and fatal VTE was 2.1% and 0.8%, respectively. Significantly, most VTE events occurred after hospital discharge, and VTE was found to be the most common cause of death at 30 days postoperatively [9].

It is a matter of concern to note that the likelihood of death in cancer patients with VTE is greater than that of patients with cancer or VTE alone [10, 11]. Moreover, in cancer patients, the possibility of complications such as anticoagulant failure, bleeding, and recurrent VTE is also higher than in patients without cancer [7, 8, 12–15].

Large population-based studies have suggested that the incidence of VTE is on the rise, among the general popula-

tion as well as the cancer-affected subgroup [2, 16]. A retrospective cohort study conducted using the discharge database of the University Health System Consortium between 1995 and 2003 reported that the increase in incidence of DVT and PE over the years was associated with black ethnicity, use of chemotherapy and also varied with the site of cancer [17].

Since VTE is becoming an increasingly frequent complication in cancer patients and contributes significantly to the morbidity and mortality among those cancer patients who are undergoing surgery, it is important to review the various aspects of its pathogenesis, prevention, and treatment.

2. Pathogenesis

There are several mechanisms due to which cancer patients are hypercoagulable, thus predisposing them to arterial and venous thromboses. The intrinsic tumor-related factors include interaction of cancer cells with monocytes and macrophages, causing release of cytokines like TNF, IL-1, and IL-6 which cause damage to the endothelial surfaces making them thrombogenic [18]. Another mechanism is by activation of the coagulation pathway. This is chiefly mediated by the expression of tissue factor (TF) on the epithelial surfaces which have undergone malignant transformation [19–21]. This glycoprotein is a procoagulant, and it has been identified to bind and activate factor VII, which in turn triggers the coagulation cascade by activating factor X and factor II [19, 22–27]. Cysteine proteases released from tumor cells also have procoagulant properties and cause direct activation of factor X [28–31]. In adenocarcinomas nonenzymatic activation of factor X occurs due to interaction with the sialic acid moieties of the mucin [32]. In addition activation of platelets (leading to aggregation) and endothelial cells (leading to overexpression of plasminogen activator inhibitor-1) and inhibition of the synthesis of anticoagulation proteins in the liver further cause dysregulation of the coagulation cascade [33–37].

Extrinsic factors such as chemotherapeutic and antiangiogenic agents also contribute to the prothrombotic state by various mechanisms [38, 39]. Chemotherapeutic drugs have been reported to damage the vascular endothelium, activate platelets, cause induction of TF in tumor cells, and downregulate anticoagulant proteins like protein C and S [40–44].

3. Risk Factors for Venous Thromboembolism in Cancer Patients

The factors that increase the risk for VTE in cancer patients may be identified to be either tumor, patient, or treatment related [45]. Tumor-related characteristics include tumor type, site, stage of disease, and duration of cancer. As per studies, the cancer types associated with the greatest risk for VTE are adenocarcinomas of the pancreas and stomach, gynecologic and hematologic malignancies, and malignant tumors of the brain, bone, lung, and kidney [9, 10, 16, 17, 46–52]. The role of extent of the disease as a potential risk factor was analyzed in a study conducted over a large cohort of 66,

329 oncologic patients. It reported a 1.9-fold increased risk for VTE in patients with metastases [48]. Similar findings of increased risk of VTE among cancer patients with metastatic disease were also reported by other studies [46, 47, 50–52].

Patient-related factors include advanced age, female gender, black ethnicity, previous history of VTE, the presence of comorbid conditions (obesity, infection, renal disease, pulmonary disease, congestive heart failure, transfusion, and prothrombotic mutations) [9, 16, 17, 46, 47, 51–60]. Treatment-related characteristics include current hospitalization, pharmacologic measures such as chemotherapeutic agents, hormonal agents, antiangiogenic agents, and erythropoiesis-stimulating agents (ESAs) and mechanical interventions such as surgery and use of central venous catheters [9, 46, 48–50, 53, 55–57, 61–80].

Predictive models for VTE have been designed which assign scores appropriate to the odds ratio of some of the most important risk factors, and thus cumulative risk can be calculated for each patient [81, 82]. The model developed by Khorana et al. shows platelet count $\geq 350000/\text{mm}^3$, hemoglobin concentration $< 10 \text{ g/dL}$, and leukocyte count $> 11000/\text{mm}^3$ as promising predictive markers for VTE in oncologic patients [82]. The risk of recurrent VTE is also higher among patients with malignancy when compared to those without cancer [8, 10, 83–85]. The recurrence risk for VTE among oncologic patients is twice as high as compared to that for healthy controls, and if the patient is receiving chemotherapy, the risk increases to four times higher [83]. This risk is reported to be fivefold higher in cancer patients with metastases while in those with localized disease the recurrence risk is two—to threefold [8].

4. Need for Primary Prevention and Modalities Available

It has been well established that the risk of postoperative VTE is almost two times greater among cancer patients than noncancer patients undergoing similar surgical procedures, despite the use of prophylaxis [86]. Without prophylaxis the risk of VTE in cancer patients undergoing surgery has been estimated to be as high as 50%, and VTE was found to be the most common cause of death in this group of patients at 30 days after surgery [9, 86]. Postoperative pharmacologic prophylaxis with anticoagulants for 1–2 weeks after major abdominal or pelvic cancer surgery can reduce the risk of VTE to 1.3% for symptomatic deep vein thrombosis (DVT) and 0.4% for fatal pulmonary embolism [87, 88]. Thus, it is evident from these data that effective thromboprophylaxis is imperative in cancer patients undergoing surgery [89]. The different modalities available for prevention and treatment are listed in Table 1.

5. Pharmacologic Prophylaxis

5.1. Aspirin. Aspirin is a nonsteroidal anti-inflammatory drug which is found to be beneficial in preventing major thrombotic vascular events in patients with atherosclerotic disease due to its antiplatelet action. But, in prevention

TABLE 1: Modalities for prevention and treatment of DVT.

Pharmacological prophylaxis		Mechanical prophylaxis
Older agents	Newer agents	
(i) Aspirin	(i) Factor Xa inhibitor	(i) Graduated compression stockings (GCS)
(ii) Warfarin	fondaparinux	(ii) Venous foot pump devices
(iii) Unfractionated heparin (UFH)	idrabiotaparinux	(iii) Electrical calf stimulation
(iv) Low molecular weight heparin (LMWH)	idraparinux	(iv) Intermittent pneumatic compression devices
dalteparin	rivaroxaban	
enoxaparin sodium	apixaban	
tinzaparin	(ii) Direct thrombin inhibitor (DTI)	
nadroparin sodium	dabigatran	
bemiparin		

of VTE in hospitalized patients, only limited evidence is available regarding its protective role [86]. Hence aspirin is not recommended as a primary modality of pharmacoprophylaxis by any of the guidelines.

5.2. Warfarin. Warfarin is a vitamin K antagonist (VKA) and interferes with the synthesis of clotting factors and thus prevents thrombosis. For over 50 years it formed an integral part of the standard anticoagulation regimen for prophylaxis and treatment of VTE. But its use has been gradually replaced by Unfractionated Heparin (UFH) and now Low Molecular Weight Heparin (LMWH). This is because, although efficacious, the use of warfarin therapy is particularly challenging for clinicians and patients in the oncologic setting. Its anticoagulant effect is of delayed onset and prolonged duration, with clearance furthered lowered in patient with hepatic insufficiency thus necessitating frequent blood sampling for laboratory monitoring in an attempt to maintain adequate, but not excessive dosing [90–93]. Achievement and maintenance of the target international normalized ration (INR) with oral warfarin is more difficult in cancer patients due to concomitant anorexia and emesis [94, 95]. Warfarin’s pharmacokinetics is also influenced by diet, and other medications besides interindividual variation [91, 96]. The need for frequent invasive procedures in some cancer patients (e.g., therapeutic paracentesis) results in interruption of anticoagulation leading to erratic INRs [91]. Warfarin pharmacokinetics is altered by interaction with chemotherapeutic agents, particularly 5 fluorouracil, fluoropyrimidines, capecitabine, erlotinib, and sorafenib leading to elevation in INR value and predisposition to bleeding [97–103]. Also cancer patients on warfarin are reported to develop recurrent thrombosis and bleeding manifestations, more frequently when compared to patients without cancer, despite close maintenance of target INR in both groups [104, 105].

5.3. Unfractionated Heparin. Unfractionated heparin (UFH) consists of a heterogenous mixture of sulphated mucopolysaccharides ranging from 3000 to 30,000 Daltons in molecular weight [106]. Some of these molecules possess a pentasaccharide sequence which binds and activates antithrombin

III in the plasma. This complex then inhibits the action of activated thrombin (factor IIa) and factor Xa and thus mediates an anticoagulant effect. UFH can be administered by either continuous intravenous infusion or by subcutaneous injection, and its effects can be rapidly and completely reversed by infusion of protamine sulfate [106, 107].

In an early prospective randomized controlled trial conducted in 178 surgical patients, using UFH as the drug for primary prophylaxis against DVT, the group treated with UFH had a 13.3% incidence of DVT, whereas in the control group it was 35.8% ($P < 0.001$) [108]. Further analysis revealed a 25%-relative risk reduction in patients without cancer and a 55% relative risk reduction in patients with cancer [108]. In a similar prospective controlled study conducted in 820 surgical patients, the incidence of VT in controls was 16%, while in the treated patients it was 4.2%, with a slight increase in minor complications reported in the treated group. Subgroup analysis showed a relative risk reduction of 18% in patients without cancer and a 39% relative risk reduction in cancer patients [109]. Thus these early trials and subsequent meta-analyses and multicentre trials strongly emphasized the benefit of UFH prophylaxis in surgical patients, especially in those patients who had concomitant cancer [89, 110].

Despite its documented efficacy in this group of patients, certain disadvantages limit the use of UFH. The pharmacokinetics of UFH are unpredictable and influenced by its binding to plasma proteins, endothelial cell surfaces, macrophages, and other acute phase reactants, thus causing variability in the anticoagulant response, which necessitates monitoring of Activated Partial Thromboplastin Time (APTT) values in patients [106, 107]. Also the interaction of UFH molecules with platelet factor 4 and generation of heparin-dependent IgG antibodies can lead to an immune-mediated complication-heparin-induced thrombocytopenia (HIT), where release of procoagulant microparticles such as thrombin occurs into the systemic circulation leads to disseminated arterial and venous thrombosis [111].

5.4. Low Molecular Weight Heparin. Low-molecular-weight heparin (LMWH) is obtained by alkaline degradation of heparin benzyl ester and consists of molecules enriched

with short chains. LMWH has a molecular weight of 4000–5000 Dalton with a higher anti-Xa:IIa ratio [106]. Due its higher bioavailability (90% versus 30%), longer half-life (4 to 6 hours versus 0.5 to 1 hour), predictable and reproducible anticoagulant response, minimal interaction with non-anticoagulant related plasma proteins, and lesser propensity to cause heparin-induced thrombocytopenia and osteoporosis, LMWH has gained popularity over UFH for use in primary and secondary VTE prophylaxis [106, 112]. Some of the routinely prescribed LMWHs include dalteparin, enoxaparin sodium, tinzaparin, nadroparin sodium, and bemiparin.

In practice, the reports from early trials comparing the efficacy and safety of LMWH and UFH suggested no significant difference in the incidence of VTE, minor and major bleeding events and death among the two groups [88, 113–122]. A meta-analysis, conducted in 2001, found that, in comparison with placebo or no treatment, LMWH was associated with a significant reduction in clinical VTE in a population of patients undergoing general surgery [123]. When compared with UFH a significant reduction in clinical VTE ($P = .049$) was found in favor of LMWH. This trend was also reflected among in patients undergoing surgery for cancer [123]. A systematic review and meta-analysis published in 2008 which included 14 trials comparing LMWH with UFH for thromboprophylaxis in patients with cancer undergoing surgery concluded that there was no significant survival benefit for LMWH compared with UFH [124]. The same group published another review and meta-analysis in 2011 which included 16 such trials and reported that no significant difference was found between perioperative thromboprophylaxis with LMWH versus UFH in their effects on mortality and embolic outcomes in patients with cancer [125]. The trials in which the study population was cancer patients undergoing major abdominal surgery are listed in Table 2.

With regard to LMWH dosage, a study was conducted comparing 2500 and 5000 units of dalteparin in 2070 patients undergoing abdominal surgery (66.4% of whom had cancer) [126]. Among patients with malignancy, the incidence of DVT was significantly lower in patients given higher dose of dalteparin (8.5% versus 14.9%, $P < 0.001$). Overall, the frequency of bleeding complications was greater in the group which received high-dose dalteparin (4.7% versus 2.7%, $P = 0.02$) but among the patients with malignancy there was no significant difference (4.6% versus 3.6%, $P > 0.05$). Currently most guidelines recommend the use of 5000 U of dalteparin for prophylaxis [127–134]. The drawbacks of LMWHs include the need for daily injection leading to higher direct costs although in comparison to UFH the overall costs are lower as they can be administered at home [112].

5.5. Factor Xa Inhibitors. Factor-specific anticoagulants such as factor Xa inhibitors have emerged as treatment alternatives to heparin and warfarin after being proven to be safe and effective. Factor Xa inhibitors are synthetic derivatives of the antithrombin-binding pentasaccharide moiety found in

UFH and LMWH. They mediate an anticoagulant effect by selective inhibition of factor Xa and are administered subcutaneously at a dose of 2.5 mg for pharmacoprophylaxis of VTE [106]. Currently, three factor Xa inhibitors have been identified: fondaparinux (the only one approved so far by the US Food and Drug Administration), idrabiotaparin, and idraparin (both in clinical trials) [134].

The important randomized studies done in surgical patients to evaluate the efficacy of fondaparinux are summarised in Table 3. In a double-blinded randomized trial conducted in 2007, a VTE rate reduction of 69.8% was demonstrated with use of fondaparinux and intermittent pneumatic compression (IPC) in patients who underwent major abdominal surgery (40% of patients were operated for cancer) when compared to treatment with IPC alone [135]. In another large randomized trial known as PEGASUS22, the efficacy and safety profiles of fondaparinux were compared with dalteparin in 2048 patients who underwent major abdominal surgery [136]. Subgroup analysis of the study's 1408 patients who underwent surgery for cancer showed rates of VTE for fondaparinux and dalteparin group to be 4.7% and 7.7%, respectively, with a relative risk reduction of 38.6% while for the entire PEGASUS population the relative risk reduction with fondaparinux was 24.6%. Incidence of major bleeding in the cancer subgroup was comparable between the two treatments.

The likelihood for development of heparin-induced thrombocytopenia (HIT) is low with the use of fondaparinux, and some case series also report treatment of HIT with 7.5 mg of fondaparinux [137, 138]. The National Comprehensive Cancer Network (NCCN) guidelines consider the use of fondaparinux for treatment of HIT as unlabeled use [130]. The American College of Chest Physicians (ACCPs) guidelines suggest that direct thrombin inhibitor (DTI) is to be used for initial treatment of HIT. Once the platelets levels recover this is to be replaced by therapeutic doses of fondaparinux and gradual bridging to warfarin therapy be done [139]. As majority of these trials and case series have been performed on noncancer patients, fondaparinux should be cautiously used for treatment of HIT in cancer patients, until further supporting evidence is available.

5.6. Newer Agents for Anticoagulation. Currently several new agents for VTE prophylaxes have been introduced into clinical practice or are in the final stages of development and testing. These include dagibatran, an oral direct thrombin inhibitor (DTI) which has been evaluated against enoxaparin in the BISTRO II, RE-MODEL, RE-NOVATE and RE-MOBILIZE trials, conducted in orthopedic surgical patients and was shown to be noninferior to enoxaparin in its efficacy and safety [140–143]. Rivaroxaban, an oral direct factor Xa inhibitor was also compared to enoxaparin in a similar patient group in the ODIXa-OD-HIP and RECORD 1–4 trials and showed superior reduction in risk of VTE with no significant increase in risk of major postoperative bleeding [144–148]. Apixaban, another oral inhibitor of factor Xa, is being evaluated in patients with cancer in ongoing trials [149, 150].

TABLE 2: Studies evaluating venous thromboembolism (VTE) prophylaxis with LMWH and UFH in cancer patients undergoing major abdominal surgery.

Trial	Method	Patients (n)	Study population	Regimen		Followup	Incidence of VTE	
				Study	Control		Study (%)	Control (%)
Bergqvist et al. 1990 [246]	Randomise double blind-trial	637	Patients with cancer (study subgroup) undergoing abdominal surgery	Dalteparin 5000 Units preoperatively then q.d. $\times$ 5–8 days	UFH 5000 Units 2 h pre-operatively then b.d. $\times$ 5–8 days	7 days	6.4	11.2
EFS 1988 [120]	Randomised trial	704	Patients with cancer (study subgroup) scheduled for elective abdominal surgery	Fraxiparin 7500 anti-Xa units preoperatively then q.d. $\times$ 7 days	Calcium heparin 5000 units preoperatively then t.i.d $\times$ 7 days	7 days		
Enoxacan 1997 [229]	Double-blind randomised trial	631	Patients undergoing planned curative abdominal or pelvic surgery for cancer (study subgroup)	Enoxaparin 40 mg q.d. $\times$ 10 days	Low-dose UFH t.i.d $\times$ 10 days	3 months	14.7	18.2
Fricker et al. 1988 [247]	Randomised trial	80	Patients with cancer undergoing surgery for abdominal and pelvic malignancy	2500 anti-Xa Units 2 h before surgery and 12 h after the first injection and then 5000 anti-Xa Units fragmin injection q.d. $\times$ 10 days	5000 IU of calcium heparin injection 2 h before the surgery and then t.i.d $\times$ 10 days	10 days	5	5
Godwin et al. 1993 [248]	Double-blind randomised trial	904	Patients undergoing abdominal or pelvic cancer surgery	RDH (Normiflo) 50 U 2 h preoperatively and then 90 U q.d./bd	UFH 5000 U 2 h preoperatively and then 5000 U b.d.			
McLeod et al. 2001 [249]	Randomise double-blind trial	324	Patients with cancer undergoing colorectal cancer surgery	Enoxaparin 40 mg q.d. $\times$ 10 days	Heparin 5000 U t.i.d. $\times$ 10 days	10 days	13.9	16.9
Onarheim et al. 1986 [250]	Randomised double-blind trial	52	Patients undergoing surgery for abdominal malignancy	Dalteparin 5000 U 2 h preoperatively then q.d. $\times$ 6 days	Heparin Kabi2165 5000 U 2 h preoperatively then b.d. $\times$ 6 days	7 days	1.92	3.84

VTE: venous thromboembolism, LMWH: low molecular weight heparin, UFH: unfractionated heparin, sc: subcutaneous.

6. Antitumor Effects of Anticoagulants

A new perspective in the use of anticoagulant agents is that, in addition to preventing thromboembolic complications, these agents also improve survival rates in cancer patients by exerting antitumor effects. This theory has been supported by evidence from studies conducted with warfarin and LMWH [151–156]. This effect seems to be mediated by immunomodulatory actions, inhibition of angiogenesis, inhibition of release of coagulation proteases, and by triggering apoptosis [157].

7. Mechanical Thromboprophylaxis

Mechanical thromboprophylaxis is generally used as an adjunct to pharmacological therapy and includes modalities like electrical calf stimulation, intermittent pneumatic compression devices, graduated compression stockings (GCSs), and venous foot pump devices which increase venous outflow and/or reduce stasis within the leg veins [86]. Early and frequent ambulation of hospitalized patients at risk for VTE also helps to reduce venous stasis and is an important principle of postoperative patient care [86]. Unlike the

TABLE 3: Studies of VTE prophylaxis with fondaparinux in patients undergoing major abdominal surgery.

Trial	Method	Patients (<i>n</i>)	Study population	Regimen		Outcome	Followup	Incidences		
				Study	Control			Study (%)	VTE control (%)	Major bleeding Study (%) Control (%) <i>P</i> value
Turpie et al. 2007 [135]	Randomized, double-blind, placebocon- trolled superiority trial	842	Patients undergoing abdominal surgery	Fondaparinux 2.5 mg sc × 5–9 days, starting 6–8 hours postoperatively with intermittent pneumatic compression	Placebo 2.5 mg sc × 5–9 days, starting 6–8 hours postoperatively with intermittent pneumatic compression	Efficacy outcome— VTE up to day 10 Safety outcomes— major bleeding and all-cause mortality	32 days	1.7	5.3	<i>P</i> = 0.004 1.6 0.2 0.006
				Dalteparin 5000 units sc q.d. × 5–9 days. The first two doses of fondaparinux, 2500 units each, were given 2 hours before surgery and 12 hours after the preoperative administration						
Agnelli et al. 2005 [136]	double-blind double-dummy randomized study	2048	Patients undergoing major abdominal surgery	Fondaparinux 2.5 mg sc q.d. × 5–9 days started 6 hours postoperatively	Dalteparin 5000 units sc q.d. × 5–9 days. The first two doses of fondaparinux, 2500 units each, were given 2 hours before surgery and 12 hours after the preoperative administration	Primary outcome— DVT detected by bilateral venography, symptomatic, confirmed DVT or PE Safety outcome— major bleeding	10 days	4.6	6.1	0.144 3.4 2.4 0.122

VTE: venous thromboembolism, DVT: deep vein thrombosis, PE: pulmonary embolism, sc: subcutaneous.

pharmacologic methods, the use of mechanical modalities does not increase the risk of bleeding, which makes it advantageous for use in patients who are at a high risk of bleeding, such as cancer patients [158–160]. When used in conjunction with the pharmacoprophylaxis, they have demonstrated an additive anticoagulant effect [161–168].

A meta-analysis published in 2001, which looked at 12 studies that had been conducted between 1992 and 1996, concluded that the use of graduated compression stockings alone for prophylaxis of VTE after moderate-risk surgery results in a significant risk reduction [169]. A review published in 2011 focused on the benefits of combination of modalities for prophylaxis [170]. Eleven studies were identified which evaluated combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of VTE in high-risk patients, of which 6 studies were randomized controlled trials, and the study population in total was 7431 patients. They concluded that in comparison with compression alone, combined prophylactic modalities decrease the incidence of VTE significantly. Also, compared to pharmacological prophylaxis alone, combined modalities reduce the incidence of DVT significantly, but the effect on PE is unknown. Unfortunately, no large clinical trials specific to its use in cancer patients undergoing surgery have been published yet. Also the existing studies are few in number, have small sample size, with high potential for bias, and have failed to evaluate specific design features of each mechanical device [132, 171, 172]. Poor patient and staff compliance and high cost of purchase and maintenance of the device are other limitations to the use of mechanical prophylaxis [173–177].

8. Duration of Prophylaxis

Traditionally, LMWH therapy was continued for a short period (1 week) following surgery in cancer patients. Later trials explored the efficacy and safety of extended (4 week) LMWH therapy in this group. The ENOXOCAN- and FAME-randomized control trials gave evidence for greater reduction in risk of VTE with extended prophylaxis, without a significant increase in the rate of bleeding or incidence of other complications [178, 179] (Table 4).

In the randomized, double-blind study CANBESURE, which enrolled patients admitted for abdominal or pelvic surgery for cancer, extended duration prophylaxis that was evaluated using bemiparin [180]. The primary efficacy outcome which was defined as the combined incidence at the end of double-blind period of total documented symptomatic and asymptomatic DVT, nonfatal PE and all-cause mortality was not significantly reduced. But there was a decrease in major VTE, which was defined as the composite of symptomatic and asymptomatic proximal DVT, nonfatal PE and VTE-related deaths, without increasing hemorrhagic complications (Table 4).

However, in a retrospective study conducted between 2003 and 2006, to assess the occurrence of symptomatic VTE after major abdominal surgery for colorectal cancer in patients in whom LMWH was continued only until hospital

discharge (median of 11 days), it was seen that among the 494 patients, only 3 (0.6%) developed symptomatic VTE in the follow-up period, despite lack of extended prophylaxis [181]. The study concluded that postoperative LMWH for a median of 11 days, combined with the use of graded compression stockings, and early mobilization provided sufficient thromboprophylaxis.

Currently most guidelines recommend extended duration of prophylaxis with LMWH (up to 4 weeks postoperatively) in cancer patients who undergo major abdominal surgery [130, 131, 182, 183].

9. Diagnosis

Prompt and accurate diagnosis of DVT is crucial since proper anticoagulant treatment is necessary to reduce the risk of early and late complications. DVT can be suspected clinically based on signs and symptoms, and several clinical decision rules have been evaluated, of which “Wells decision rule” is the most widely tested and used clinical decision rule [184]. However, clinical diagnosis alone is insufficient because of poor sensitivity and specificity. Cogo et al. studied the role of compression ultrasound in patients with clinically suspected DVT and found that only one in four patients suspected of having DVT actually has the disease [185]. Therefore, an objective diagnosis is necessary to avoid the risk of denying treatment to patients in need or giving potentially harmful treatment to patients who do not need it [186].

10. Clinical Decision Rules

The Wells rule consists of nine items which can be obtained by medical history and physical examination [184]. On point is given for each item, and two points are deducted when an alternative diagnosis is considered more likely than DVT (Table 5). The decision rule initially divided patients into a low risk (0 points), an intermediate risk (1–2 points), and a high risk (3 or more points). However, it has been recently modified into two groups, namely, low probability (<2 points) or high probability (2 or more points) of DVT [187]. The main drawback of the Wells rule is that it is not completely objective, due to the subjective element of considering an alternative diagnosis [188]. Current role of this clinical decision rule in the diagnosis of DVT is to guide further investigation.

11. D-Dimer Testing

D dimers generated by fibrinolysis of a thrombus has a molecular weight of 1,80,000 Daltons and its *in vivo* half life is 4 to 6 hours [189]. Several D-dimer assays are available with different sensitivities and specificities which recognize these D dimers by monoclonal antibodies. Assays with intermediate sensitivity and specificity are semi-quantitative latex (sensitivity 61–100%, specificity 22–92%), qualitative latex (sensitivity 77–87%, specificity 100–100%), and whole blood assay (sensitivity 53–100%, specificity 20–94%) [190]. Assays with high sensitivity and low specificity are enzyme-linked

TABLE 4: Studies evaluating extended duration of VTE prophylaxis with LMWH in cancer patients undergoing major abdominal surgery.

Trial	Method	Patients (n)	Study population	Regimen		Followup		VTE		Incidences		Major bleeding	
				Study	Control			Study (%)	Control (%)	P value	Study (%)	Control (%)	P value
Bergqvist et al. (ENOXACAN II) [178]	RCT, Double-blinded, venography	332	Patients undergoing elective surgery for abdominal or pelvic cancer	Enoxaparin 40 mg q.d. × 6–10 days, then enoxaparin 40 mg q.d. × 19–21 days	Enoxaparin 40 mg od × 6–10 days, then placebo × 19–21 days	At 31 days		4.8	12	0.02	0.8	0.4	>0.99
						3 months		5.5	13.8	0.01	1.2	0.4	0.62
Rasmussen et al. (FAME) [179]	RCT, assessor- blinded, venography	198	Major abdominal surgery for cancer	Dalteparin 5000 IU q.d. × 1 week then dalteparin 5000 IU q.d. × 4 weeks	Dalteparin 5000 IU q.d. × 1 week then placebo × 4 weeks	4 weeks		8.8	19.6	0.03	NR	NR	NR
Kakkar et al. (CANBESURE) [180]	randomized, double-blind study, bilateral venography	1113	Major abdominal or pelvic surgery for cancer	Bemiparin 3500 IU sc q.d. × 8 days then bemiparin 3500 IU sc q.d. × 20 days	Bemiparin 3500 IU sc q.d. × 8 days then placebo × 20 days	20 days		10.1	13.3	0.26	0.6	0.3	P > 0.05

VTE: venous thromboembolism, RCT: randomized controlled trial, sc: subcutaneous.

TABLE 5: Wells' prediction score for clinical diagnosis.

Clinical feature	Points
Active cancer (ongoing treatment or within last 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of lower extremities	1
Recently bedridden for >3 d and/or major surgery within 12 wk using regional or general anaesthesia	1
Local tenderness	1
Thigh and calf swollen	1
Calf swelling 3 cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema	1
Dilated superficial veins (nonvaricose) symptomatic leg only	1
Previous documented DVT	1

2 points deducted if alternative diagnosis is more likely than DVT.

Total points: >2: DVT likely.

Total points: <2: DVT unlikely.

immunosorbent assay (sensitivity 50–100%, specificity 5–82%), enzyme-linked fluorescence assay (sensitivity 88–100%, specificity 5–82%), and quantitative latex (sensitivity 57–100%, specificity 26–97%) [190]. Since D-dimer levels are increased in other conditions like infection, inflammation, cancer, surgery and trauma, extensive burns or bruises, ischemic heart disease, stroke, peripheral artery disease, ruptured aneurysm, aortic dissection, and pregnancy, it has low specificity in diagnosing DVT [191]. Since the main aim of D dimer testing is to rule out DVT, tests with high sensitivity are preferred for routine use.

12. Imaging

Both invasive (ascending venography or phlebography) and noninvasive modalities (ultrasonography, impedance plethysmography, computed tomography, and magnetic resonance imaging) are available for confirmation of diagnosis of DVT.

13. Ascending Venography

Ascending venography is still the gold standard for the diagnosis of DVT. Contrast medium is injected in a dorsal superficial vein of the foot, and serial radiograms are taken as the contrast medium flows cranially in the deep vein system. The diagnosis of DVT is confirmed with the finding of a constant intraluminal filling defect on two or more views. Treatment can be withheld safely when a technically adequate contrast venogram shows no evidence of DVT [192]. However, invasive nature of the technique, adverse reactions, and venous endothelial toxicity following contrast administration are well-known problems with ascending venography [193]. Furthermore, contrast venography is associated with a variation in interpretation in up to 10% of the cases and is relatively expensive [194]. Hence contrast venography is now seldom used for the diagnosis of DVT.

14. Ultrasonography

Ultrasonography (US) has become a widely accepted as a primary diagnostic procedure for the work-up of clinically

suspected DVT. Initial attempts to diagnose DVT by visualization of a thrombus is associated with poor sensitivity since visibility of clot is dependent on the age of the clot. A fresh clot may appear almost anechoic and go unnoticed by visual inspection leading to under diagnosis [195]. Hence compression ultrasonography is commonly used in the radiological diagnosis of a first episode of clinically suspected DVT. In this technique, the femoral and popliteal veins are directly visualized and subsequently assessed for their compressibility in the transverse plane (two-point CUS). When a thrombus is present, compression of the vein is not possible even with a more firm pressure. This noncompressibility of the vein is established as a criterion for the diagnosis of DVT. Noncompressibility of either the femoral or popliteal vein, or both, is diagnostic for a first episode of acute proximal DVT in patients suspected of DVT with a sensitivity of 93.8% (95% CI, 92–95.3%) and a specificity of 97.8% (95% CI, 97–98.4%) [196]. The interobserver agreement of CUS is excellent for proximal DVT of the leg [197]. Hence, currently CUS is first choice of imaging modality in the diagnostic workup of patients with a first episode of clinically suspected DVT of the lower extremities.

15. Impedance Plethysmography

Impedance plethysmography evaluates the efficiency of venous outflow by means of the electrical impedance variation of the lower limbs [198]. While it is noninvasive and easy to apply, it has two major limitations; impedance plethysmography cannot identify nonoccluding DVT, and therefore it is less useful in subjects with modest or absent clinical symptoms, since these patients frequently have nonoccluding DVT. Besides it is not useful in distal DVT and is limited to symptomatic subjects with proximal DVT [199]. With the advent of US impedance plethysmography is hardly used in the diagnosis of DVT.

16. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

CT currently is used for the diagnosis of pulmonary embolism (PE) [200]. Given that DVT is the single most

TABLE 6: Comparison of VTE pharmacoprophylactic recommendations laid down by ASCO, ACCP, NCCN, National Guideline Clearing House, and ESMO.

	Guideline last updated in	Unfractionated heparin	Drug			Duration
			Dalteparin	Enoxaparin	Fondaparinux	
ASCO [127]	2007	5,000 U sc every 8 hours	5,000 U sc daily	40 mg sc daily	2.5 mg sc daily	Up to 7–10 days postop. Up to 4 weeks post op in high risk patients
ACCP [129]	2008	5,000 U sc every 8 hours	5,000 IU sc daily	40 mg sc daily	Not recommended	Up to 4 weeks after discharge
NCCN [205]	2011	5,000 U sc every 8 hours	5,000 IU sc daily	40 mg sc daily	2.5 mg sc daily	Up to 4 weeks postop
ESMO [128]	2011	5,000 U sc every 8 hours	5,000 U sc daily	40 mg sc daily	2.5 mg sc daily	Up to discharge or until ambulatory
National Guideline Clearinghouse [204]	2011	5,000 U sc every 12 hr postop	2,500 units sc 1–2 hr preop, then every 24 hr	40 mg sc 2 hr preop, then every 24 hr	Not recommended	Up to 4 weeks postop

VTE: venous thromboembolism, ASCO: American Society for Oncology, ACCP: American College of Chest Physicians, NCCN: National Comprehensive Cancer Network, ESMO: European Society Of Medical Oncology; LMWH: low molecular weight heparin, sc: subcutaneously, postop: postoperatively.

important risk factor for PE, combining pulmonary CT and CT of the pelvic veins and lower limb veins improves sensitivity and specificity. In a recent meta-analysis, a pooled sensitivity for CT venography was 96% (95% CI, 93–98%) with a pooled specificity of 95% (95% CI, 93.6–96.5%) [201]. The disadvantages of CT are the high cost, difficulty when repeat scans are needed, the need to inject higher volumes of contrast medium when pulmonary angiography and venography are combined (with a higher risk of renal toxicity), and higher exposure to radiation especially to the ovaries or testicles in younger subjects.

MRI allows the visualization of proximal DVT with satisfactory accuracy, and it allows the diagnosis of the thrombotic extension into the iliac veins and the vena cava [202]. MRI is an alternative to venography in patients with an allergy to contrast medium or other contraindications to contrast media and/or renal insufficiency. The pooled sensitivity and specificity of MR-venography were reported to be 91.5% (95% CI, 87.5–94.5%) and 94.8% (95% CI, 92.6–96.5%), respectively [203].

Currently these techniques are recommended in patients with suspected DVT and in whom US cannot be performed or is less reliable, such as patients with morbid obesity, patients in casts and patients with a suspected DVT in the iliac veins or inferior vena cava.

17. Guidelines for VTE Prophylaxis in Cancer Patients Undergoing Major Abdominal Surgery

17.1. American Society for Clinical Oncology (ASCO). After extensive review of literature and clinical trials, the American society for Clinical Oncology laid down a set of guidelines in 2007 for VTE prophylaxis in cancer patients [127]. Pharmacologic prophylaxis with either low dose UFH or LMWH was recommended for all cancer patients undergoing major abdominal surgery. Thromboprophylaxis is relatively contraindicated in patients with active uncontrollable bleeding,

active cerebrovascular hemorrhage, dissecting or cerebral aneurysm, bacterial endocarditis, pericarditis, active peptic or other GI ulceration, severe uncontrolled or malignant hypertension, severe head trauma, pregnancy (contraindication for use of warfarin), heparin-induced thrombocytopenia (contraindication for use of heparin, LMWH), and epidural catheter placement. The prophylaxis should be commenced preoperatively and continued for at least 7–10 days postoperatively. Patients with high-risk features such as residual malignant disease postoperatively, obesity, and previous history of VTE are candidates for prolonged postoperative prophylaxis (4 weeks) [127]. Details of pharmacoprophylaxis are outlined in Table 6.

17.2. European Society of Medical Oncology. The European Society of Medical Oncology brings out guidelines on VTE prophylaxis which are revised every year. The most recent supplement was brought out in 2011, and the recommendations are in keeping with those laid down by the ASCO [128]. Details of pharmacoprophylaxis are outlined in Table 6.

17.3. American College of Chest Physicians. The American College of Chest Physicians (ACCP) updated their recommendations regarding VTE prevention in patients undergoing surgery for cancer in 2008. Based on evidence from randomized controlled trials, in cancer patients undergoing general surgery, prophylaxis with low-dose UFH 5,000 U three times daily or with LMWH > 3,400 U daily (translates to 5,000 IU daily for dalteparin and 40 mg daily for enoxaparin) is strongly recommended. Also postdischarge prophylaxis for patients who have undergone major cancer surgery is recommended [204]. Details of pharmacoprophylaxis are outlined in Table 6.

17.4. National Guideline Clearing House. A Compendium of Consensus Recommendations from the American Academy of Chest Physicians (AACCP), the American Society of

Regional Anesthesia and Pain Medicine (ASRA) and American Academy of Orthopedic Surgery (AAOS) for the thromboembolic prophylaxis of adult hospitalized patients were chartered under the National Guideline Clearing house in 2010 in association with the Institute for Clinical Systems Improvement (ICSI). The updated eighth edition was released in September 2011. It differed from the ASCO guidelines in not recommending the use of fondaparinux [204]. Details of pharmacoprophylaxis are outlined in Table 6.

17.5. National Comprehensive Cancer Network. The National Comprehensive Cancer Network (NCCN) guidelines are a statement of consensus of its authors with respect to their views of currently accepted approaches to prophylaxis and treatment of VTE in adult cancer inpatient with a diagnosis of (or clinical suspicion for) cancer. It differs from other guidelines in permitting use of tinzaparin for pharmacoprophylaxis [205]. Details of pharmacoprophylaxis are outlined in Table 6.

17.6. Guidelines on Mechanical Prophylaxis. The commonly employed mechanical methods of thromboprophylaxis include graduated compression stockings (GCSs), intermittent pneumatic compression (IPC) devices, the venous foot pumps (VFPs), and Inferior Vena cava filters. The ASCO, ESMO, AACP and NCCN guidelines state that mechanical methods may be used in conjunction with the pharmacologic methods in high-risk patients (patients with recurrent pulmonary embolism) despite adequate anticoagulant treatment or with a contraindication to anticoagulant therapy (i.e., active bleeding and profound, prolonged thrombocytopenia), and are recommended as monotherapy only in cases where pharmacologic measures are contraindicated due to high risk of active bleeding [127–129, 204, 205]. Once the risk decreases the ACCP recommend that the mechanical method be substituted/supplemented by a pharmacologic agent [129]. The ACCP guideline further recommends that patients receiving these methods be subjected to careful attention to ensure proper use and to maintain their compliance with these methods [129].

18. Treatment of VTE in Cancer Patients

The chief objectives of treatment are to prevent the extension of DVT, the occurrence of pulmonary embolism, recurrence of VTE, and to prevent long-term VTE and PE complications such as postthrombotic syndrome and chronic thromboembolic pulmonary hypertension.

When compared to general medical patients, treatment of VTE in cancer patients is more challenging due to the higher frequency of recurrence and bleeding complications (despite appropriate anticoagulation and well-maintained International Normalized Ratio (INR)) [7, 10, 206–209]. The conventional protocol of treatment has been 5–7 days of therapeutic dose of UFH, followed by long-term treatment with Vitamin K antagonists (VKA) for a minimum of 3 months, titrated to an INR of 2.0–3.0 [91, 210]. But the

limitations of warfarin and UFH use, as described in the previous section, have shifted focus on LMWH as the chief modality of treatment. Comparison of different LMWH such as dalteparin, enoxaparin, and tinzaparin with warfarin, and UFH has been carried out in trials which have significantly demonstrated superior efficacy and safety profiles of LMWH for treatment of VTE in cancer patients and hence guidelines currently recommended LMWH for initial and long term treatment of acute VTE in cancer patients [127–129, 204, 205].

Trials have also been conducted to evaluate the role of direct thrombin inhibitors such ximelagatran and factor Xa inhibitors like fondaparinux in VTE treatment [211, 212]. In the THRIVE study on 2489 patients (13% of whom had cancer), it was reported that oral fixed dose ximelagatran was as effective as enoxaparin/warfarin for treatment of DVT with or without PE and showed similar rates of bleeding though other systemic side effects observed with ximelagatran are a cause for concern [211]. Post hoc analyses of the Matisse-DVT and Matisse-PE trials aimed to compare efficacy and overall survival of fondaparinux with LMWH and UFH in the initial treatment of 237 cancer patients with DVT and 240 cancer patients with PE, respectively [212]. In the DVT subgroup analysis, results showed a trend towards higher rates of recurrent VTE in fondaparinux-treated patients than enoxaparin-treated patients (12.7% versus 5.4%; $P = 0.046$) [212]. In the PE subgroup analysis, results showed higher rates of recurrent VTE in the UFH group when compared with the fondaparinux group (17.2% versus 8.9%, $P = 0.054$) [212]. In both analyses, no difference in bleeding and overall survival was observed.

19. Guidelines for VTE Treatment in Cancer Patients

The recommendations made by ASCO, NCCN, and ESMO guidelines for initial and long-term treatment of VTE in patients with cancer are listed in Table 7.

Recurrent VTE in a cancer patient despite adequate anticoagulation might be indicative of progression of the malignancy. For treatment of such patients, the options include shift to treatment with LMWH/UFH (if previously on long-term treatment with VKA), increase target INR to 3.5, or consider the use of inferior vena cava filter if recurrent PE despite adequate long-term LMWH [213]. The option of increasing the dose of LMWH in cancer patients with recurrent VTE has also been recently explored [214].

20. Evaluation of Use of Venous Thromboembolism Prophylaxis in Clinical Practice

The higher likelihood of development of VTE in surgical oncology patients has been well enumerated, and the benefit offered by prophylactic measures has been documented. Also a large number of evidence-based clinical guidelines and expert recommendations have been laid down in this context. Yet an underuse of these preventive measures

TABLE 7: Comparison of VTE treatment recommendations laid down by ASCO, NCCN, and ESMO for patients with cancer.

	Unfractionated heparin	Initial treatment of established VTE				Long-term treatment		
		Enoxaparin [#]	Dalteparin [#]	Fondaparinux [#]	Tinzaparin	Duration	Dalteparin	Warfarin
NCCN [205] & ASCO [127]	80 U/kg IV bolus, then 18 U/kg/h IV (adjust level based on PTT ^{††})	1 mg/kg sc every 12 hours 1.5 mg/kg sc daily	100 U/kg sc every 12 hours 200 U/kg sc daily	<50 kg, 2.5 mg sc daily 50–100 kg, 5 mg sc daily 100 kg, 7.5 mg sc daily	175 U/kg sc daily	For at least 5–7 days or until INR is in the therapeutic range for 2 consecutive days if changing to warfarin.	200 U/kg sc daily for 1 month; then 150 U/kg sc daily	5–10 mg PO daily; adjust dose to INR 2–3 when LMWH unavailable
	5000 IU bolus, then 30 000 IU continuous infusion over 24 h (adjust level based on PTT ^{††})	100 U/kg sc twice daily	200 U/kg sc once daily	NR	NR	For at least 5–7 days	150 U/kg sc daily	NR
ESMO [128]								

VTE: venous thromboembolism, ASCO: American Society for Oncology, NCCN: National Comprehensive Cancer Network, ESMO: European Society of Medical Oncology, IV: intravenously, sc: subcutaneously, po: orally, PTT: partial thromboplastin time, INR: international normalized ratio, NR: not recommended. [#] Significant renal clearance; avoid in patients with creatinine clearance 35 mL/min or adjust dose based on antifactor Xa levels. [†] PTT: Partial Thromboplastin time range of 1.5 to 2.5 the control value is commonly used. The best approach is to determine the PTT therapeutic range using the local method, to correspond to a heparin level of 0.3 to 0.7 U/mL using a chromogenic Xa assay.

persists, as evident from the results of some recent studies [215–219].

In a retrospective medical record review conducted in 2000, among the 495 patients (71.3% of whom had cancer) who had undergone major abdominal surgery, only 25.4% had received prophylaxis which conformed to the 1995ACCP criteria [218]. In the global Fundamental Research in Oncology and Thrombosis (FRONTLINE) study of 2001, conducted by distributing questionnaires to clinicians involved in cancer care, the knowledge and practice of VTE prophylaxis was reviewed for 3891 clinicians worldwide. Analysis showed that only 52% of the respondents routinely prescribed thromboprophylactic measures for cancer patients undergoing surgery [219]. Also of concern is the continued use of aspirin as a prophylactic agent by almost 20% of the physicians, despite the lack of supporting evidence to do so [219]. A large scale survey was conducted in the United States between 2003 and 2007 where in data on VTE prophylactic practices in oncologic patients undergoing surgery was collected using the Perspective database in an attempt to identify factors which influence the variability in the same. The data published in 2011 showed that, in a total of 252,950 patients, 79% received some form of prophylaxis, and in 46% of patients this was pharmacologic. Also it was noted that rates of prophylaxis were significantly higher in high volume hospitals and patients under therapy with high volume surgeons [220].

Also of concern is the lack of extended prophylaxis in practice, despite evidence from trials and guidelines which reaffirm its benefit. In a prospective study (ESSENTIAL) conducted at 14 Swiss hospitals, of the 1046 cancer patients included in the study, 30% underwent major cancer surgery. More than 95% of them received appropriate in hospital prophylaxis, but only 23% were given prescriptions for extended pharmacological prophylaxis at discharge. Also the median duration of prescription among those who received it was 23 days, lower than the recommended 28 days [221].

20.1. Reasons for Poor Implementation of Guidelines. Most of the barriers to effective and comprehensive implementation of prophylactic measures are attributed to physician-related factors [222]. There is a lack of awareness among physicians about the extent of risk of VTE involved in such patients and of the currently recommended management strategies [223]. Lack of familiarity and in some cases, agreement with the recommendations issued in the guidelines, along with the lack of confidence and motivation to alter existing practice patterns are common hindering factors [224]. Also certain erroneous notions like “increased risk of bleeding occurs with anticoagulant therapy in patients with cancer due to underlying procoagulant milieu created by the malignant state” are still fostered by physicians, despite evidence from studies proving good safety profile of LMWH and UFH [225–232]. Additionally the presence of multiple guidelines with varied protocols makes it confusing and complicated for physicians to follow [224]. The need for official approval and funding for the recommended drugs adds to the inconvenience faced by physicians and hence leads to the underuse of prophylaxis [224].

20.2. Improving the Implementation of Guidelines. To tackle these hurdles in implementation and bring about increased thromboprophylaxis rates and better outcomes for patients, quality improvement strategies [233, 234] have been proposed and employed such as the following.

20.2.1. Continuing Medical Education. Conducting workshops/presentations for health care providers, nurses, and pharmacists to stress on the importance of prophylaxis and to update their understanding of it has been shown to improve thromboprophylaxis rates and reduce the prevalence of VTE [162, 235–238]. By engaging recognized opinion leaders in the process of knowledge dissemination, physician practicing habits may be significantly influenced and changed [239–241].

20.2.2. Clinical Audits and Feedback. Active forms of interventions such as conducting audits and providing feedback have been shown to have the potential to alter physician's practice, improve their adherence to guidelines, and have an upper hand compared to passive techniques like educational mailings [239, 240]. In a UK study, the adherence to hospital policy on use of compression stockings and heparin in orthopedic joint replacement surgery patients was evaluated twice, three months apart, with feedback being provided to health care providers after the initial assessment. Comparison of quality of implementation of hospital protocol evaluated on both occasions revealed an improvement following the feedback session [242].

20.2.3. Clinical-Decision Support Tools. Computer-based reminders/alerts have shown great potential in making prescription of VTE prophylaxis measures more convenient, accurate, and frequent and thus reducing the incidence of VTE in hospitalized patients who are at risk for thrombosis [243]. An alternative option of using preprinted prophylaxis reminders/risk assessment models/guidelines on drug charts/hospital admission forms has also shown improvement in the use of anticoagulants in practice [236, 244].

20.2.4. Role of Supervising Organizations. Quality improvement organizations such as the National Quality Forum, the Surgical Care Improvement Project, the Agency for Healthcare Research and Quality, and the Joint Commission play a major role in bridging the gap between clinical guidelines and their implementation. Multipronged programs have to be planned and initiated to improve VTE prophylaxis rates. Also simplified guidelines such as the pocket guide developed by Investigators against Thromboembolism (INATE) initiative for orthopedic and trauma surgery serve to resolve inconsistencies between guidelines and present them in a more convenient format [245]. No individual quality improvement strategy method has proven to be singularly exceptional in its effectiveness, and studies show that an integration of several techniques yields best results [162, 236–238].

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