Venous Thromboembolism in Gynecological Malignancy

Abigail Cohen, BMedSci, BMBS, Chung Sim Lim, PhD, FRCS, and Alun Huw Davies, MA, DM, FRCS, DSC, FHEA, FEBVS, FACPH

Objective: Venous thromboembolism (VTE) is a recognized complication of gynecological malignancy and represents a leading cause of morbidity and mortality in these patients. The review aimed to discuss the incidence, risk factors, and clinical presentation of VTE before examining the literature on the diagnosis, prevention, and management in the context of uterine, cervical, ovarian, and vulval cancers.

Methods/Materials: A literature search was performed using Ovid Medline and Embase with the following words: "gynecological malignancy," "pelvic tumor," "venous thromboembolism," "deep vein thrombosis" and "pulmonary embolism."

Results: The incidence of VTE in patients with gynecological malignancy ranged between 3% and 25% and was affected by several patient and tumor factors. Duplex ultrasonography is currently the first-line imaging modality for deep venous thrombosis with sensitivity and specificity of up to 95% and 100%, respectively. Low-molecular-weight heparin is currently the VTE prophylaxis and treatment of choice for patients with gynecological malignancy, although warfarin and unfractionated heparin play a role in selected circumstances. The relatively new direct oral anticoagulants including factor Xa inhibitors and direct thrombin inhibitors are increasingly being used, although further evaluations are required, particularly in cancer patients. Catheter-directed thrombolysis and percutaneous mechanical and surgical thrombectomy may have a role in treating patients with severe symptomatic iliocaval or iliofemoral deep venous thrombosis. Overall, VTE is a poor prognosis marker in patients with gynecological malignancy.

Conclusions: Gynecological malignancy–associated VTE is associated with significant morbidity, contributing to a large number of life years lost. Although promising new therapies are emerging, a 2-pronged approach is required to simultaneously target cancer-specific management and predict early on those who are likely to be affected. In the meantime, clinicians should continue to combine current guidelines with a multidisciplinary team approach to ensure that these complex patients receive the best evidence-based and compassionate care.

Key Words: Venous, Thromboembolism, Gynecological cancer, Pulmonary embolism

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Academic Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London, Charing Cross Hospital, London, United Kingdom.

Address correspondence and reprint requests to Alun H. Davies, Charing Cross Hospital, Fulham Palace Rd, London W6 8RF, United Kingdom. E-mail: a.h.davies@imperial.ac.uk.

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Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) are well-recognized complications of gynecological malignancy and represent a leading cause of morbidity and mortality in these patients.[1] Although current guidelines state that low-molecular-weight heparins (LMWHs) form the cornerstone of treatment,[2] gynecological oncology patients present a potential minefield of complicating factors surrounding tumor pathology, associated treatment, and increased bleeding risk. Although the pathogenesis underlying the development of

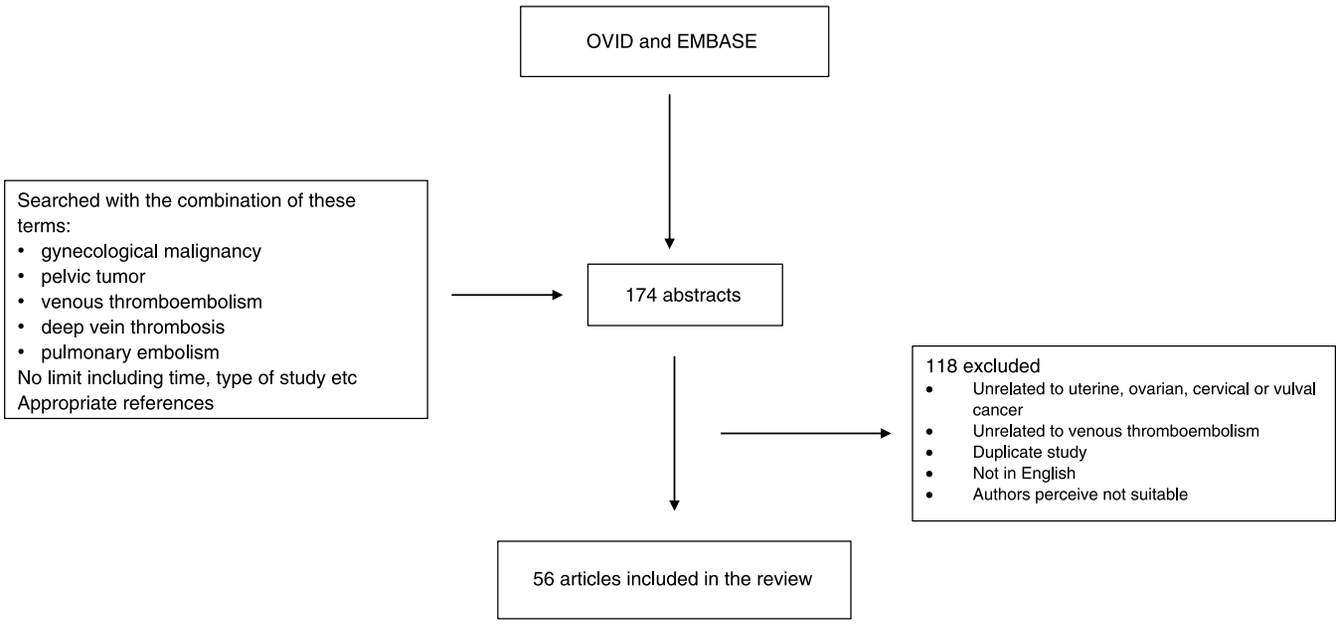

FIGURE 1. Flow diagram summarizes the results of the literature search and the number of articles included and excluded.

VTE is similar between major types of gynecological cancers, there are complexities surrounding the epidemiology, etiology, clinical presentation, and disease stage, which also affect optimal management. The consequential life years lost, in addition to myriad financial and social implications, dictates that its amelioration should remain a high clinical priority.

This narrative review explores current literature surrounding VTE within the context of the 4 major types of gynecological cancers: ovarian, uterine, cervical, and vulval cancer. It discusses the incidence, risk factors, and pathogenesis and summarizes available evidence related to clinical presentation and management. Ultimately, it aims to highlight where further research and formal trials are required to ensure that clinicians are delivering the best possible patient care.

METHODS

A literature search was performed using Ovid Medline and Embase with the following words: "gynecological malignancy," "pelvic tumor," "venous thromboembolism," "deep vein thrombosis" and "pulmonary embolism." A total of 174 abstracts were identified and then reviewed for their suitability, looking specifically for those containing the terms "uterine cancer," "ovarian cancer," "cervical cancer," or "vulval cancer." Inclusion criteria were broad and involved all study types, human and animal models, and prospective and retrospective reviews with no time limit. Appropriate references from qualifying articles were also used. Articles that had not been translated into English were excluded, as were abstracts that had not resulted in peer-reviewed publication. Figure 1 summarizes the results of the search and the number of articles were included and excluded in the review.

EPIDEMIOLOGY

There is huge disparity in the reported incidence of VTE in patients with gynecological malignancy, ranging between 3% and 25% across their life-span. It is likely that a variety of variables affect the conveyed incidence, which notably include the type of malignancy, the stage, and whether or not the patient has commenced treatment.[3] However, the range in incidence will also be influenced by the method of diagnosis; clinical diagnosis will be significantly lower than diagnosis made by venogram or 125-fibrinogen uptake testing (Table 1). One large American study including 853 cancer patients (among which were 289 cervical, 195 ovarian, 255 uterine, and 36 vulvar) found the overall incidence of DVT to be 4.2%[4] A further nationwide study in Taiwan of 1013 patients with cervical cancer found the incidence of VTE to be 3.3%[5] However, incidence figures for cervical cancer had been quoted as high as 11.7%[1] A small Japanese study reported the pretreatment incidence of DVT and DVT + PE in endometrial cancer as 9.9% and 4.7%, respectively.[6] The incidence quoted for ovarian cancer in a study of more than 13,000 women in the California cancer registry was 5.2%.[7] However, figures as high as 25% have been reported pretreatment.[3] The broad range is likely due to heterogeneity of population groups and study designs. The incidence relating specifically to vulval cancers is largely missing from current literature.

ETIOLOGY/RISK FACTORS

Virchow triad, encompassing hypercoagulability, hemostasis, and endothelial injury, illustrates the 3 general categories under which most well-known risk factors for VTE in malignancy will fall (Fig. 2). Despite incongruence in specific numerical figures, it is abundantly clear that malignancy itself is an independent risk factor for development of VTE. Data consistently show up to a 7-fold increased risk of VTE in cancer patients compared with the general population.[2,4] Furthermore, 10.5% of patients presenting with an idiopathic VTE will have a diagnosis of cancer within 5 to 10 years, with the majority diagnosed in the first year.[8]

TABLE 1. A summary of studies looking at the incidence of the different types of gynecological malignancy

Study	Design	Type of Cancer	Incidence of DVT/VTE, %	Method of Diagnosis
Santoso et al[4]	Prospective cohort study	Cervical, ovarian, uterine, and vulvar	4.2	Doppler ultrasonography
Tsai et al[5]	Prospective cohort study	Cervical	3.3	Not specified
Jacobson et al[1]	Retrospective data analysis	Cervical	11.7	Variable
Satoh et al[6]	Prospective cohort study	Endometrial cancer	9.9	D-dimer, Doppler ultrasonography, and pulmonary scintigraphy
Rodriguez et al[7]	Retrospective data analysis	Ovarian	5.2	Variable

Within the gynecological cancer cohort, certain personal patient characteristics have been shown to be significant risk factors, particularly age, with patients older than 60 years having a 4-fold increased risk compared with their younger counterparts (10.4% vs 2.6%.).[3] Although high body mass index (>30 kg/m^2) is generally considered a risk factor for development of VTE, small studies specifically looking at patients with gynecological malignancy have not been able to demonstrate it to be a significant risk factor.[9] Specific tumor factors including type, size, and stage were also implicated in the risk profile. Considering cervical cancer, tumors of greater than 50 mm increased the risk of VTE by almost 9 times (10.2% >50 mm vs 1.2% <50 mm,) as did being Federation of Gynecology and Obstetrics stage IV (27.8% stage IV vs 3.2% stages I-III.)[3] It was concluded that the increased risk is likely due to the large pelvic tumor size impairing venous return, causing hemostasis and therefore a predisposition to clotting.[3] In two studies of ovarian and endometrial carcinoma, clear cell histology and massive ascites were shown to be important risk factors in the former, nonendometrioid and extrauterine spread noteworthy in the latter.[6,10]

In addition to the tumor-related risk factors, the treatment of gynecological malignancy presents a heterogeneous source of VTE risk. It is generally accepted that surgery is integral to most treatment regimes in locally advanced disease, with adjuvant chemotherapy and radiotherapy added for those with high-risk tumors (large tumors, deep invasion, lymph node invasion).[11] Nevertheless, surgery itself is a risk factor for VTE,[12] although the incidence quoted varies considerably from 0% to 17%.[13–16] In one of the largest studies looking at 397 patients who underwent radical abdominal hysterectomy for cancer, 2.7% developed a VTE.[13] By comparison, the incidence of VTE after open hysterectomy for benign conditions was only 0.6% (81/12,733 patients).[17] Postoperative PE remains the primary cause of mortality after gynecological cancer surgery.[18]

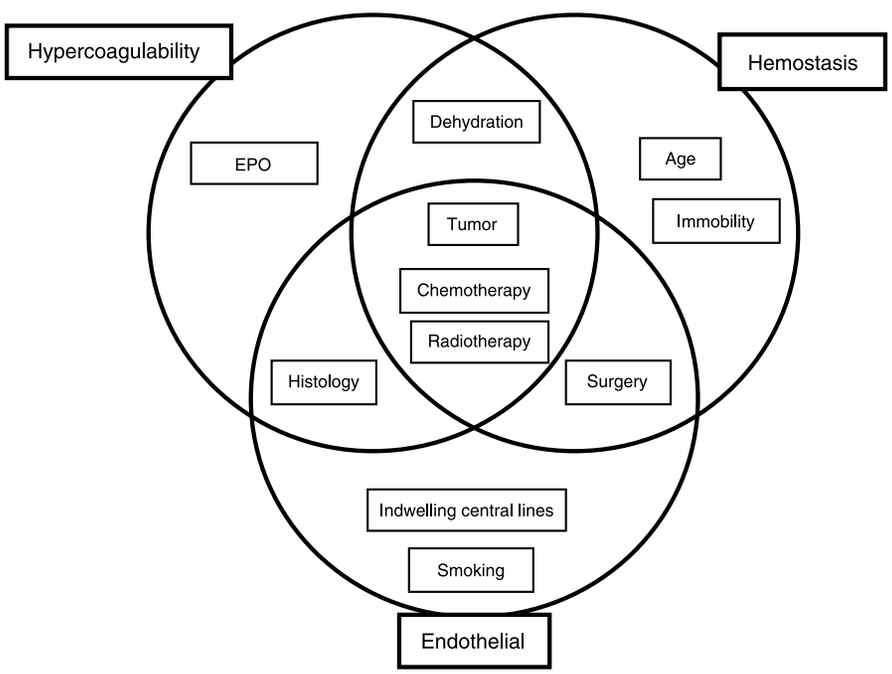

FIGURE 2. Venn diagram illustrates how risk factors for VTE can be classified within the Virchow triad.

Although chemotherapy increases survival in patients with high-risk tumors, it also carries a significant VTE risk.[12] A large American study looking at incidence of VTE among cancer patients undergoing chemotherapy found that in the 12 months after initiation of treatment, 12.6% overall developed a VTE (compared with just 1.4% in the control group.)[19] Looking specifically at those with ovarian cancer, the incidence of VTE in the chemotherapy group was 11% (the highest incidence was in pancreatic cancer at 19.2% and the lowest was bladder cancer at 8.2%.)[19] The type of agent used also seems to affect incidence. Cisplatin particularly is thought to trigger platelet aggregation and thromboxane formation through the activation of platelet phospholipase A2.[20] In the study mentioned previously, cisplatin and bevacizumab were associated with the highest risk of VTE (odds ratios, 1.36 [95% confidence interval, 1.19–1.55] and 1.43 [95% confidence interval, 1.24–1.65], respectively).[19]

Although it is suspected that damage to the pelvic venous plexus during radiotherapy may increase the risk of VTE, there is limited data available quoting specific incidence or explaining the mechanism. However, a prospective study of 411 gynecology patients identified previous pelvic radiation therapy as a statistically significant risk factor in the development of DVT.[21] Similarly, in one early trial assessing mortality associated with gynecological brachytherapy, the incidence of VTE among 329 women after treatment was 1.2%.[22]

Assessing risk of complication forms an important part in assessing any new cancer therapy. A large Gynecologic Oncology Group trial of erythropoietin-stimulating agents to treat malignancy-induced anemia had to be stopped early because of a 19.3% incidence of VTE in the treatment group compared with 7.7% in the control group.[23]

Beyond the statistical figures, it has been speculated that the true incidence may in fact be higher than reports suggest.[23] The National Cancer Institute Common Toxicity Criteria, which reports on complications of cancer therapies, includes VTE in the same category as arterial disease, thus masking true rates. In addition, people may falsely attribute the thrombotic event as a complication of cancer rather than treatment.[23]

PATHOGENESIS

It is widely documented in the literature that cancer growth is linked with the production of a hypercoagulable state (Fig. 3).[24] Histopathological specimens from tumors have demonstrated fibrin strands and platelet plugs around tumors suggesting employment of coagulation cascade by aggressive tumors to confer rapid growth.[25] Broadly speaking, there are three key mechanisms behind this phenomenon.[24,26–28] First, through substantial tissue factor release, malignant cells facilitate significant procoagulant, fibrinolytic, and proaggregating activity.[28] Second, they release proinflammatory and proangiogenic cytokines including tumor necrosis factor and interleukin 1.[28] Third, they have high expression of adhesion molecules, such as integrins, cadherins, and selectins interacting directly with host vascular and blood cells.[27] The latter two result in activation of the host's procoagulant and proadhesive cells, which simultaneously down-regulate anticoagulant response.[28] The main cells involved in this process are endothelial cells, platelets, and leukocytes. The consequence of combined activation of these pathways is enhanced thrombin and fibrin production and thus a prothrombotic state.[28] This is further supported by a study that looked at specific markers of coagulation in cancer-associated DVT. Results demonstrated significantly greater levels of procoagulants (thrombin-antithrombin complex, prothrombin 1 + 2, and von Willebrand fragment antigens) in the cancer DVT group than in the DVT control group.[29]

This, however, is only part of the story, as the Virchow triad highlights two additional factors in the pathogenesis of thrombus formation; hemostasis and endothelial injury. Large pelvic tumors can compress pelvic veins impeding venous return, causing hemostasis and subsequent thrombus formation.[23] Moreover, larger cervical tumors are more likely to invade the parametria and pelvic wall potentially damaging endothelial cells.[23] Beyond the cancer itself, supposed therapies can contribute to thrombus production. For example, chemotherapy is known to cause endothelial damage, with bleomycin causing immediate impact on endothelial cell integrity.[27] Reduced mobility associated with surgery results in decreased pump action of the gastrocnemius resulting in further pooling and hemostasis.

CLINICAL PRESENTATION AND DIAGNOSIS

As a common and potentially serious complication of gynecological malignancy, it is imperative that clinicians are familiar with the common presenting symptoms of DVT and PE. One study involving 893 patients with malignancy (including gynecological, breast, and anal cancers) found that

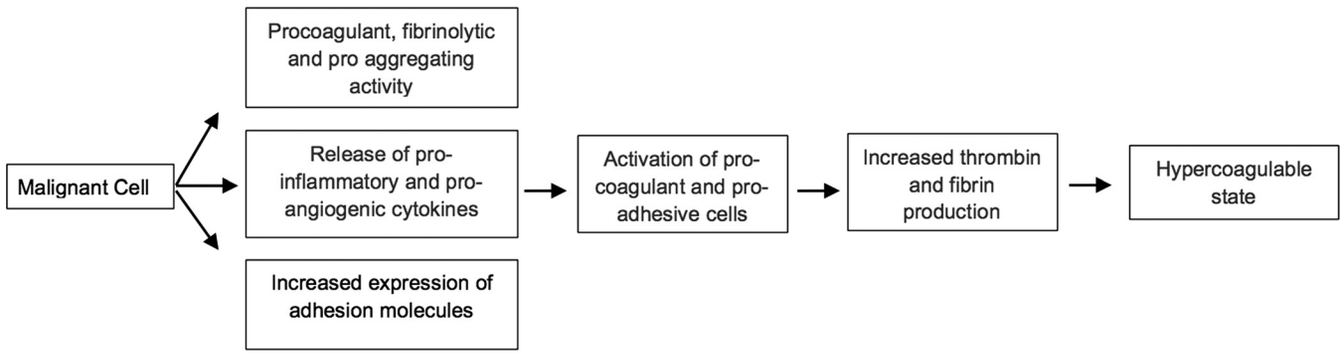

FIGURE 3. Flowchart demonstrates how malignant cells produce a hypercoagulable state.

leg edema, erythema, and warmth were the symptoms most likely to indicate a DVT ($P < 0.008$, $P < 0.009$, and $P < 0.001$, respectively[4]). Conversely, pain and bilateral leg complaints showed a poor correlation with presence of DVT.[4] A further study concluded that 50% to 80% of patients with textbook symptoms such as erythema and swelling will not have a DVT because the symptoms do not carry good specificity.[30] In terms of PE, the classic symptoms of hemoptysis and pleuritic chest pain seem to be rare. In a study of 72 patients, the 8 patients found to have a PE on pulmonary scintigraphy were all asymptomatic.[10] Therefore, clinicians should have a low threshold to investigate further if there is suspicion of VTE, even in the absence of textbook symptoms.

In some patients, a DVT or PE can be the first presentation of an occult malignancy. Often, these cases can be severe with bilateral DVT, recurrent DVT, or iliofemoral DVT. Review of studies reported a 2- to 5-fold increased risk of occult cancer in patients with idiopathic VTE, with this risk being particularly elevated for malignancy of certain inner organs including the ovary, brain and pancreas.[31] So far, the proportion of patients diagnosed as having idiopathic VTE who have gynecological malignancy is unclear. However, ovarian cancer is one of the most common malignancies associated with VTE. Occasionally, there can be more unusual manifestations of the hypercoagulable state associated with malignancy. One case report outlined microtumor embolus leading to severe cor pulmonale.[32] Likewise, vascular paraneoplastic syndromes are rare but may present as the first manifestation of underlying gynecological malignancy.[31]

Compression vein ultrasonography with color Doppler flow or duplex ultrasonography is the most frequently used test in the diagnosis of DVT.[33] Although operator specific, the sensitivity and specificity ranges have been reported between 82% and 96% and 97% and 100%, respectively.[34] The modality has other advantages in that its cheap, reproducible, and noninvasive, particularly compared with traditional venography.[34] Other imaging modalities such as computed tomography (CT) and magnetic resonance venography with relatively high sensitivity and specificity are also increasingly being used particularly to assess for iliofemoral DVT, although duplex ultrasonography should remain the first-line investigation. Catheter venography, which used to be the criterion standard investigation, should only be used when interventional treatment such as thrombolysis is planned because of its invasiveness.

In the diagnosis of PE, CT pulmonary angiography remains the criterion standard.[35] However, CT venography has been examined in combination with CT pulmonary angiography to assess the diagnostic impact of examining the pelvic veins simultaneously during the scan. Results demonstrate a small increase in percentage of patients diagnosed; however, risk-benefit ratio of this marginal increase remains controversial.[36]

D-dimer is a fibrin degradation product present after a blood clot has been degraded by fibrinolysis and levels are frequently elevated in cancer patients even in the absence of VTE. Although extensive testing has been undertaken to investigate the role of D-dimers in predicting VTE, the results thus far limit its use to exclusion of VTE in patients with a D-dimer level lower than 1.5 μg/mL; this has a negative predictive value of greater than 95%.[37] Its sensitivity and specificity for isolated DVT are 84% and 50%, respectively, thus limiting its use as a diagnostic tool.[37]

PREVENTION

Venous thromboembolism, even in high-risk cancer patients, is considered one of the most common causes of preventable hospital death.[38] In terms of prophylaxis to be initiated just before gynecological procedures, the ninth edition of the American College of Chest Physician guidelines (2012) are summarized in Table 2.[35] Because all patients with cancer are classed as high risk, they should be receiving low molecular weight heparin (LMWH), low-dose unfractionated heparin, intermittent pneumatic compression (IPC), or graduated compression stockings.[35] The highest-risk patients having extensive procedures should have pharmacological and mechanical prophylaxis.[35] A study looking at the cost-effectiveness of IPC with and without LMWH in gynecological oncology patients concluded that when used together, the average cost per life year saved (GBP £33,962) for a women with stage 3 ovarian cancer was above the threshold for which the intervention would be considered cost-effective.[30] Considering preoperative prophylaxis, one study found that of 101 patients with gynecological malignancy who received LMWH before their laparotomy, only 2 (0.02%) developed a postoperative DVT.[39] By comparison, in the group who did not receive preoperative LMWH, 11 (0.07%) of 138 developed a DVT.[39] Moreover, DVT-attributable deaths were lower in the LMWH cohort.[39]

Evidently, although it is clear that most gynecology oncology patients benefit from combined prophylaxis, there are certain exceptions. Patients with brain metastasis may be subjected to lengthy operations involving large wounds and high bleeding risk.[40] The guidance for these patients is to

TABLE 2. Summary of American College of Chest Physician guidelines on VTE thromboprophylaxis

	Minor Procedure	Laparoscopic Procedure	Major Procedure
Low risk	Early ambulation	Early ambulation	LMWH* just before surgery and while patient is immobile
Moderate risk	LMWH*	LMWH*	LMWH*
High risk	LMWH*	LMWH* until discharge from hospital	LMWH* until discharge from hospital and possibly for 28 days after

*Where LMWH is contraindicated low-dose unfractionated heparin should be considered as an alternative.

commence UFH (due to its reversibility such as with protamine) within 24 hours after operation once the patient is stable and to continue only until the patient is ambulatory.[40] In complex patients, a careful risk/balance calculation should be undertaken with the inclusion of appropriate specialties including gynecologist, hematologist, oncologist, and vascular specialists to formulate the appropriate regimen.[33]

TREATMENT

Considering that patients with gynecological malignancy are thought to have one of the highest thrombosis risks,[41] there are remarkably few trials looking specifically into their management. Current guidelines advocate LMWHs as preferred treatment of VTE (both DVT and PE) in cancer patients.[2] The National Institute of Health and Care Excellence in the United Kingdom recommends to offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months. After 6 months of LMWH, the risks and benefits of continuing anticoagulation need to be reassessed (National Institute of Health and Care Excellence CG144).[42] Vitamin K antagonists (warfarin) are a reasonable alternative where there are contraindications to LMWH, but in long-term treatment, LMWH demonstrates superior safety and efficacy.[2] Low-molecular-weight heparin also holds advantages over warfarin in that it has a shorter half-life and more predictable pharmacokinetic profile,[2] both characteristics that are expedient in unpredictable cancer patients. There is also laboratory-based evidence emerging that LMWH may hold some antineoplastic properties. Several mechanisms have been proposed for this action including induction of tissue factor pathway inhibitor, inhibition of chemokine receptors, or prevention of angiogenesis.[43] However, clinical trials specifically in gynecology patients are required before this additional advantage can be confirmed.

Although most available guidelines focus on postoperative management of VTE, a reasonable number of patients with gynecological malignancy will have a silent VTE before surgery.[44] One study reported the incidence to be as high as 25% in patients with ovarian cancer and 9.9% in patients with endometrial cancer.[6] It is unclear whether or not treatment as per American College of Chest Physician guidelines is adequate in this complicated subset of patients.[44] Presurgical, asymptomatic DVT most often involves the crural vessels, and for these patients, it has been suggested that both UFH and IPC should be commenced preoperatively and continue postoperatively to reduce the risk of pelvic DVT.[44] In addition, for those with symptomatic VTE before surgery, the high risk of PE and consequential right heart strain warranted involvement of cardiologist and possible placement of inferior vena cava filter.[44]

Inferior vena cava filters can be used in cancer patients to prevent PE where hemorrhage risk precludes the use of anticoagulation.[45] One study looking at inferior vena cava filter insertion for 15 years found no statistical difference in survival times.[45] However, in those who could be anticoagulated after insertion, life expectancy was improved (hazard ratio, 0.45, $P < 0.003$[45]). Inferior vena cava filter is also indicated in patients with recurrent PEs despite adequately anticoagulated.

Direct oral anticoagulants (DOACs), which specifically inhibit components of the coagulation cascade, have great potential in the treatment of VTE in cancer patients, with certain advantages over their older counterparts (Table 3).[2] Regarding factor Xa inhibitors (apixaban, rivaroxaban) and direct thrombin inhibitors (dabigatran,) phase 3 randomized controlled trials have demonstrated noninferiority of all 3 agents when compared with standard regimes in the prevention of recurrent VTE.[46–49] A recent meta-analysis of 6 randomized controlled trials comparing the efficacy of warfarin with the

TABLE 3. Brief comparison of warfarin vs LMWH vs DOAC[2]

Anticoagulant	Mechanism of Action	Advantages	Disadvantages
Warfarin	Vitamin K antagonist	(1) Time proven (2) Easily reversible	(1) Multiple drug interactions (2) Frequent venipuncture (3) Cost associated with monitoring
LMWH	Indirect thrombin inhibitors	(1) Predictable effect even in gastrointestinal disturbance (2) Safe in pregnancy (3) Avoids frequent venipuncture	(1) Daily injections (2) Risk of osteoporosis and thrombocytopenia (3) Cost associated with district nurses (4) Diminished renal function
DOAC	Factor Xa inhibitors (rivaroxaban, apixiban) Direct thrombin inhibitors (dabigatran)	(1) No need for frequent venipuncture or daily injections (2) Initial trials have demonstrated equivalent efficacy (3) Does not require regular monitoring (4) Fixed dose	(1) Inadequate data around use in cancer patients (2) Not easily reversible

DOACs found that of 1132 cancer patients included, incidence of recurrent VTE was 3.9% in patients taking a DOAC and 6% in patients taking warfarin.[50]

For more severe episodes of VTE, some additional treatments may be beneficial. For the subset of patients who develop acute iliofemoral DVT, there is a role for catheter-directed thrombolysis (CDT). In the appropriate setting, it has been shown to reduce incidence of post–thrombotic syndrome (overall risk reduction of 14.4%) as well as maintaining iliofemoral patency at 6 months (66% patency in the CDT group compared with 47% in the conventional therapy group, $P = 0.012$.[51]) Where CDT is contraindicated or severe forms of DVT, such as phlegmasia cerulean dolens are present, surgical or percutaneous mechanical thrombectomy may be required.[52] However, once again, specific data detailing efficacy and safety of these treatments in cancer patients are lacking.

PROGNOSIS

It is quite clearly documented in multiple articles spanning decades that developing a malignancy-associated VTE is linked with a poorer prognosis. In one large 7-year study of cervical cancer patients, the 5-year survival for those who did not have a VTE was close to 80%, whereas survival for those who did was just less than 40%.[1] The article concluded that patients who do not develop a VTE survive longer on average ($P < 0.0001$).[1] A further study examining 1-year survival demonstrated an equally poor prognosis, with just 12% of cancer-associated VTE patients surviving compared with 36% of those with cancer who did not develop a VTE ($P < 0.001$).[53] Multivariate analysis demonstrated a 2-fold increased risk of dying in cancer patients with a DVT; cervical cancer and VTE seemed to hold an especially poor prognosis ($P < 0.01$).[54]

That said, death in these patients is usually linked to tumor progression rather than the thrombotic event. Therefore, it is postulated that the poorer prognosis attributed to these events is due to their being a marker of severe and aggressive tumor biology.[1] Indeed, the incidence of VTE is often highest in those initially diagnosed as having metastatic disease.[55] Adjusting for patient variables, diagnosis of VTE is a significant predictor of reduced survival time.[55]

DISCUSSION AND FUTURE PERSPECTIVE

It is clear from current literature that VTE is prevalent in patients with gynecological malignancy and that it is undoubtedly associated with increased morbidity and overall a poorer prognosis.[56] This considered, it is surprising that trials looking specifically at the management of VTE in cancer patients are sparse. Moreover, although gynecological malignancy presents one of the biggest thrombosis risks, data pertaining to VTE management in this subset of patients is woefully inadequate. Although LMWH is currently considered the cornerstone of prophylaxis and treatment, newer anticoagulant agents may hold the potential to create safe, predictable treatment regimens for cancer patients with minimal interactions and adverse effects.[46–49] Despite this, all the large DOAC trials include only small cohorts of cancer patients (Table 4).

In addition, these trials excluded patients with end-organ dysfunction or increased bleeding risk such that included patients may not be representative of those with progressive cancer.[2] It is crucial therefore that further cancer-specific trials are undertaken to ensure that treatment of VTE in this important subgroup is backed by an updated evidence base.

Likewise, although we now hold a good understanding of how malignancy contributes to a hypercoagulable state, it is not yet understood why some high-risk patients will never go on to develop a VTE, whereas others will. There is scope for further investigation of coagulation abnormalities in cancer patients, with the ultimate aim of producing a reliable test that may predict from coagulation studies which patients are likely to develop a VTE. This will allow for targeted management. Similarly, a deeper comprehension of basic and translational science may allow for the creation of more specific anticoagulant drugs.

This review highlights several important and novel concepts. The review found that studies that specifically investigated VTE in the context of gynecological malignancy are relatively uncommon despite it being a common complication with high morbidity and mortality. The current understanding and management of VTE in gynecological malignancy is largely based on studies on solid cancers in general. Relatively few and smaller studies on VTE specifically on gynecological malignancy, as reviewed in this article, seem to provide more in-depth understanding; hence, further larger and well-designed research in this area is clearly needed. The review also shows that the pathophysiology of VTE in gynecological cancers is complex and varies with tumor type, grade and stage, and oncological treatment received. Therefore, understanding this specifically may help in VTE risk stratification to identify which patient may benefit from more aggressive treatment or precautions for VTE. The findings of this review also stress the importance of diagnosing and aggressively preventing and treating VTE in gynecological malignancy due to its debilitating and poor prognostic effect. Finally, the recent introduction of DOACs likely affects the management of VTE in gynecological malignancy, although again, further specific studies are still needed.

In summary, malignancy-associated VTE is associated with significant morbidity, contributing to a large number of life years lost and imposing huge financial strain on the health care services such as the National Health Service in the United

TABLE 4. Percentage of cancer patients included in the biggest trials of novel anticoagulant agents

Trial	Anticoagulant Investigated	% of Patients with Malignancy Included
RE-COVER[48]	Dabigatran	4.8
RE-MEDY[49]	Dabigatran	2.1
EINSTEIN DVT[41]	Rivaroxaban	6
EINSTEIN PE[50]	Rivaroxaban	4.6
EINSTEIN EXT[51]	Rivaroxaban	4.5
AMPLIFY[52]	Apixaban	2.7
AMPLIFY ETX[52]	Apixaban	1.1

Kingdom. Although promising new therapies are emerging, a 2-pronged approach is required to simultaneously target cancer-specific management and predict early on those who are likely to be affected. In the meantime, clinicians should continue to combine current guidelines with a multidisciplinary team approach to ensure that these complex patients receive the best evidence-based and compassionate care.

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