Venous thromboembolism in cervical cancer

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Venous thromboembolism (VTE) is common in malignant disease and is associated with substantial morbidity and mortality. Recently, VTE has received increased attention as a result of the use of newer drugs, such as erythropoietin-stimulating agents or antiangiogenic drugs, which increase the risk of this condition. Several reviews have been published on VTE in cancer, but none have specifically focused on cervical cancer. In this review, we focus on the incidence of VTE, patient, tumour, and treatment-related risk factors for VTE, and treatment and prevention of VTE in the setting of cervical cancer.

Introduction

Cervical cancer is a common and lethal malignant disease. Although its incidence is decreasing in industrialised countries, it is still a common cause of death in developing countries. This disease is highly curable in the early stages, and, provided no dissemination to distant organs has occurred, cure is also possible in the more advanced stages.

The challenge in the management of cervical cancer, as with all cancers, is optimising the therapeutic ratio—ie, how much toxicity is acceptable for continued improvement in local control or survival? New approaches to managing this disease include new drugs alone or in combination with existing treatments, such as radiotherapy or chemotherapy, or new combinations of existing conventional treatments. Any of these approaches can be associated with increased toxic effects.

Oncologists recognise venous thromboembolism (VTE) as a common problem in patients with cancer (figure 1), and one that is associated with substantial morbidity and mortality.[1,2] Recently, VTE has received increased attention as a result of the use of newer drugs, such as erythropoietin-stimulating agents,[3] and antiangiogenic drugs, which increase the risk of VTE.[4] Several reviews of VTE in cancer have been published,[5–8] but none have specifically focused on this condition in the setting of cervical cancer. This article reviews the incidence of VTE, patient, tumour, and treatment-related risk factors for VTE, and treatment and prevention of VTE in the setting of cervical cancer.

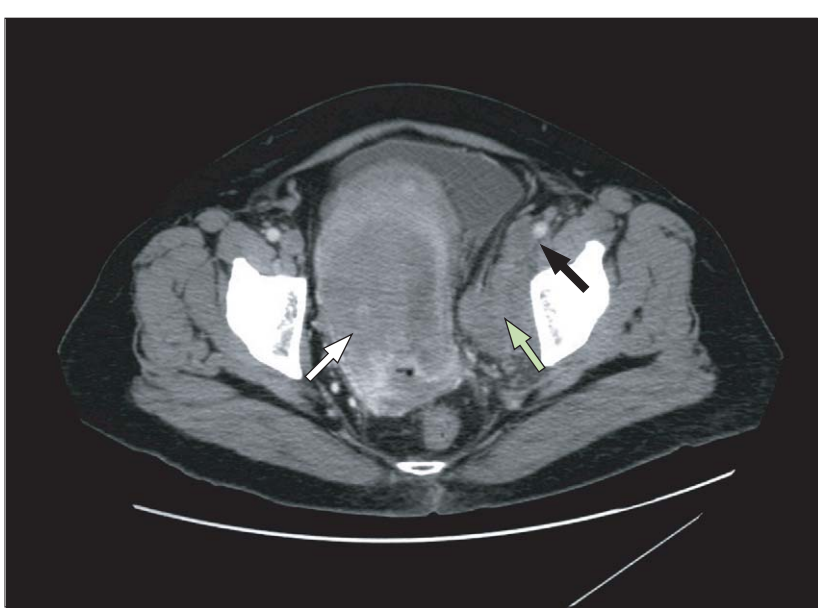

Figure 1: **Large cervical cancer (white arrow), enlarged lymph node on the pelvic-side wall (green arrow), and thrombosis in the left femoral and iliac veins (black arrow) in a patient who presented with vaginal bleeding and left leg swelling**

Incidence

Reports of the incidence of VTE in patients with cervical cancer vary widely, ranging from 0% to 34%. This broad range is, in part, due to heterogeneous patient populations in individual studies. However, differences in study methods are also likely to be a factor. Prospective studies are better suited for documenting treatment-related toxic effects than retrospective studies, because they can specify the frequency of follow-up and whether or not VTE was detected in the course of usual follow-up or by specific testing used to screen for this condition.

Concerns have been raised that substantial underreporting of VTE in cervical cancer might be occurring.[9] In addition to issues surrounding identification of a VTE event, the way in which VTE events are documented and reported is not consistent. Many toxicity scores combine cardiac and vascular events. For example, the US National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 includes myocardial infarction, hypertension, and arterial ischaemia in the same category as VTE. Even when vascular events are reported separately, distinguishing VTE from other vascular events is not possible, as shown by the NCI common terminology criteria for adverse events (CTCAE) version 3, which separates cardiac and vascular events, but does not separate VTE from other vascular toxic effects.[10] Furthermore, VTE might be considered a complication of malignant disease rather than a treatment-related toxic effect, which can lead to episodes being overlooked.

Risk factors

The classic triad of risk factors for VTE, attributed to Virchow,[11] includes hypercoagulability, venous stasis, and vessel trauma. Several patient, tumour, and treatment-related risk factors for VTE in cervical cancer also exist, many of which relate to this triad.

Patient-related risk

No reports exist that describe patient-related risk factors for VTE in cervical cancer. However, several such risk factors have been described for VTE in other settings, and are likely to be the same as those in cervical cancer. These risk factors include age,[12–15] sex,[12,14,16] personal history of cancer[13,15] previous VTE,[13–16] congestive heart failure,[13,16] and immobilisation,[13,16] among others. Inherited traits, such as Factor V Leiden deficiency or prothrombin 20210A mutation, have also been identified as important risk factors for VTE in patients with cancer,[5] although again, these risks have not been specifically studied in cervical cancer.

Tumour-related risk

The risk of VTE probably varies according to several tumour-related factors, but detailed information for these factors is not available. For example, the effect of a specific type of tumour cell on the incidence of VTE in cervical cancer is unknown. Most cervical cancers are squamous-cell carcinomas, with adenocarcinomas being the second most common. Findings from other cancer sites suggest that mucin-producing tumours (eg, pancreatic tumours) are associated with a high risk of VTE in these settings.[7,17,18]

Another tumour-related factor for which little information exists is the effect of cancer stage on the incidence of VTE. In cervical cancer, disease stage is defined by the extent of tumour spread to the parametria or pelvic side wall. The proximity of the tumour to the pelvic veins affects the chance of venous compression and stasis. Enlarged nodal masses, usually located on the pelvic side wall, can cause the same problems (although nodal involvement is not included in the International Federation of Gynecology and Obstetrics staging system for cervical cancer[19]). Venous stasis has been proposed to increase the risk of VTE. In a study of patients with cervical cancer undergoing surgery, concentrations of von Willebrand factor, fibrinopeptide A, and D-dimer were measured to identify activation of the coagulation cascade. An increase in these concentrations was noted in patients with advanced-stage disease.[20] The clinical implication of this specific finding is unknown, but clinical findings from the general cancer population show an increased risk of VTE in advanced-stage disease.[21]

A discussion of VTE in relation to cancer of any origin needs to include the cancer-related hypercoagulable state. Although VTE is the clinical manifestation of a hypercoagulable state, coagulation can be increased in cancer without VTE, and might still contribute to worse outcomes. The molecular relation between cancer and thrombosis has been well described.[18,22–24] Tissue factor and cancer procoagulant are two of the most important contributors to this hypercoagulable state. Tissue factor, a transmembrane glycoprotein produced by endothelial cells as part of a physiological reaction to endothelial-cell damage, is a potent stimulator of coagulation. In the pathological state of malignant disease, tissue factor is abundantly secreted by both tumour cells and tumour-associated endothelial cells and macrophages. Cancer procoagulant, a cysteine proteinase growth factor that is only secreted by malignant cells and is not normally found in the body, also stimulates coagulation. To our knowledge, no studies have specifically described the expression of tissue factor or cancer procoagulant in patients with cervical cancer.

Other physiological processes that are changed in cancer, and contribute to a hypercoagulable state include: inflammatory response to the tumour;[7,18,22] increased platelet activation and aggregation;[7,22] and a disrupted fibrinolytic system.[7,22]

Treatment-related risk

Although the presence of a tumour increases the risk of VTE, anticancer treatment can also increase this risk. In North America, surgery alone is the treatment of choice for early-stage invasive cervical cancer. The standard curative surgical procedure is a (modified) radical hysterectomy and pelvic-lymph-node dissection (PLND). Locally advanced tumours are treated with concurrent chemoradiotherapy with intention to cure,[25–28] and adjuvant radiotherapy or chemotherapy can be added after surgery if high-risk factors (ie, tumour size, depth of invasion, and lymphatic space invasion) are present.[29,30] In certain favourable situations (eg, small tumour size), when the preservation of fertility is a concern, radical trachelectomy and PLND can be done, which involves removal of the cervix and parametria, while leaving the uterus intact. In other countries, planned trimodality treatment is often used, even for advanced-stage disease. Furthermore, surgery now has an increasingly laparascopic approach in some countries.

However, surgery itself can be a major risk factor for VTE.[13,14,16] Pulmonary embolism is considered to be the leading cause of postoperative death after gynaecological cancer surgery.[31] The incidence of VTE after such surgery varies between 0% and 17% (table 1).[32–40] To our knowledge, only one prospective study[33] exists on the association of VTE with gynaecological cancer surgery. In this randomised controlled trial, 168 patients scheduled to undergo traditional radical hysterectomy were assigned to either extraperitoneal PLND, transperitoneal PLND, or laparoscopic PLND. No difference in the incidence of deep-vein thrombosis was noted between the three groups, with an overall incidence of 6% being recorded.[33] A large retrospective single-centre study[38] included 397 patients with early-invasive cervical cancer and showed that 2·8% of patients were diagnosed with VTE.

The mechanism of VTE development in association with surgery seems to involve vessel damage. The trauma of surgery exposes the subendothelium and tissue factor, and induces the release of cytokines, all of which activate the coagulation cascade.[5,22]

	Patients, n	Study design	Treatment	Prophylaxis	Incidence of VTE, n (%)
Martino et al[32]	72	Single-institution review	Major abdominal surgery	Intermittent pneumatic compression	PE=2 (3)
Benedetti Panici et al[33]	168	RCT of three different methods of PLND with RAH	Neoadjuvant chemotherapy followed by RAH with either extraperitoneal, transperitoneal, or laparascopic PLND	LMWH	Overall: DVT=9/150 (6); Extraperitoneal: DVT=3/50 (6); Transperitoneal: DVT=2/48 (4) Laparascopic: DVT=4/52 (7)
Jackson et al[34]	100 (50 cases and 50 controls)	Case–control	Cases: LARVH Controls: RAH	All patients had perioperative LMWH and intraoperative pneumatic stockings	Cases: PE=0 (0); Controls: PE=1 (2)
Benedetti Panici et al[35]	42 (all with stage III disease)	Single-institution review	Neoadjuvant chemotherapy followed by type IV or V RAH	NA	7 (17) (PE=4 [10]; DVT=3 [7])
Greer et al[36]	55 (all with adenocarcinoma)	Single-institution retrospective review	RAH plus PLND	NA	PE=1/55 (2)
Leath et al[37]	23	Single-institution retrospective review	Aborted RAH, subsequently given radiotherapy with or without chemotherapy	NA	DVT=1 (4)
Sivanesaratnam et al[38]	397	Single-institution review	RAH plus PLND	None	11 (3) (PE=2 [0·5]; DVT=9 [2])
Steed et al[39]	276	Single-institution review	RAH or LARVH	NA	RAH: DVT=1/205 (0·5); LARVH: DVT=1/71 (1·4)
Landoni et al[40]	343 (stage Ib or IIa disease)	RCT	RAH or radiotherapy	NA	RAH: PE=1/169 (0·6)

PE=pulmonary embolism. RCT=randomised controlled trial. PLND=pelvic lymph-node dissection. RAH=radical abdominal hysterectomy. LMWH=low-molecular-weight heparin. DVT=deep-vein thrombosis. LARVH=laparascopic-assisted radical vaginal hysterectomy. NA=not available.

Table 1: **Incidence of VTE in patients with cervical cancer treated with surgery**

In advanced disease, the addition of chemotherapy to radiotherapy has shown an 8% improvement in overall survival.[41] However, despite the benefits of chemotherapy for outcome, it is also a well-recognised risk factor for VTE.[13,17] Unfortunately, although many reports exist on the addition of chemotherapy to radiotherapy for the treatment of advanced-stage cervical cancer,[25–29,42] none specifically report the incidence of VTE.

Although the optimum chemotherapy regimen for concurrent treatment is not known, the most commonly used regimen is cisplatin alone or in combination with fluorouracil. Cisplatin is associated with several vascular toxic effects, including arterial and venous thrombosis, hypertension, myocardial infarction, Reynauds syndrome, and stroke.[43–45]

An understanding of the underlying mechanisms of chemotherapy-related VTE has not been achieved although a number of effects have been described,[7,17] including: increased concentrations of procoagulant proteins; reduced concentrations of natural anticoagulants; suppression of fibrinolytic activity; increased platelet reactivity and activation; enhanced adhesion of neutrophils; suppression of the protein C pathway; release of procoagulants and cytokines from lysed tumour cells.[7]

Radiotherapy is also a probable risk factor for VTE, but its association with VTE has been poorly studied compared with chemotherapy and surgery. One randomised study[40] that compared the effects of surgery with radiotherapy in early-stage cervical cancer reported the occurrence of one pulmonary embolism in the surgical group (n=169) compared with none in the radiotherapy group. No deep-vein thromboses were reported in either group.

An essential component of curative radiotherapy for cervical cancer is intracavity brachytherapy, which is given in addition to external-beam radiotherapy. This technique involves instrumentation of the uterus under conscious sedation or general anaesthesia and immobilisation of the patient for hours or days to plan and deliver treatment.

Incidences of VTE reported in the published work for patients receiving brachytherapy range from 0% to 17% (table 2).[3,40,46–53] The only prospective data are from the studies by Thomas and colleagues,[3] Landoni and co-workers,[40] and Lambin and co-workers,[49] although patients in the latter study also had surgery. In the study by Thomas and colleagues,[3] 8% of patients with cervical cancer were diagnosed with VTE. However, a large retrospective single-institution review,[48] which included 4043 patients, reported a VTE incidence of less than 1%. This value is suspiciously low and raises the question of missed or poorly documented events.

The disruptive and inflammatory effect of radiotherapy on the vasculature has been described in the published work.[54,55] Radiotherapy leads to endothelial-cell disruption, release of cytokines, increased platelet aggregation, and leucocyte accumulation.[54,55] Furthermore, a small study of 42 patients with cervical cancer and 20 patients with uterine cancer all of whom underwent radiotherapy, noted a modest transient rise in thrombin during treatment.[56]

Hypoxia and anaemia are prominent features of cervical cancer and are thought to contribute to

	Patients, n	Study design	Treatment	Prophylaxis	Incidence of VTE, n (%)
Thomas et al[3]	109	RCT	Chemoradiotherapy with or without erythropoietin-stimulating agent	None	Without ESA: 4/52 (8)
Landoni et al[40]	343 (stage Ib or IIa disease)	RCT	RAH or radiotherapy	NA	Radiotherapy: 0/158 (0)
Corn et al[46]	100	Single-institution review	External radiotherapy and brachytherapy	72% had unfractionated heparin, compression elastic stockings, or external pneumatic calf compression	PE=1 (1)
Jacobson et al[47]	48	Single-institution retrospective review	Chemoradiotherapy	NA	8 (17) (DVT=3 [6], PE=4 [8], arterial thrombosis=1 [2])
Jhingran and Eifel[48]	4043	Single-institution retrospective review	Low-dose-rate brachytherapy as part of treatment (98% also had external-beam radiotherapy)	Before 1978 compression elastic stockings and exercises used, after this date unfractionated heparin used	11 (0·3) (DVT=3 [0·07], PE=8 [0·2])
Lambin et al[49]	204	RCT	Two low-dose rates of brachytherapy tested; brachytherapy plus RAH and adjuvant external radiotherapy given if LN+	NA	2 (1)
Lanciano et al[50]	91 with cervical brachytherapy insertions	Single-institution retrospective review	Brachytherapy. Use of external-beam radiotherapy not stated	70% had unfractionated heparin, compression stockings, or external pneumatic calf compression	0 (0)
Temkin et al[51]	68	Single-institution retrospective review	Chemoradiotherapy with or without ESA depending on year	NA	Without ESA: 2/45 (4)
Wun et al[52]	147	Single-institution retrospective review	Chemoradiotherapy with or without ESA depending on year	None	Without ESA: 2/72 (3)
Potter et al[53]	48	Single-institution retrospective review	Chemoradiotherapy; brachytherapy was three-dimensional	NA	3 (6) (DVT=2 [4], PE=1 [2])

RCT=randomised controlled trial. RAH=radical abdominal hysterectomy. NA=not available. PE=pulmonary embolism. DVT=deep-vein thrombosis. LN=lymph nodes.

Table 2: **Incidence of VTE in patients with cervical cancer treated with radiotherapy**

radiotherapy and chemotherapy resistance. Increasing the concentration of haemoglobin is postulated to overcome tumour hypoxia and mitigate such resistance; thus, patients with cervical cancer who are undergoing curative radiotherapy are commonly transfused to a haemoglobin concentration of more than 100 g/L. A large retrospective nationwide Canadian study[57] showed that the average weekly nadir haemoglobin concentration was strongly prognostic for outcome in patients undergoing radiotherapy. Patients who were transfused up to 120g/L had the same prognosis as those who maintained their hemoglobin on their own.[57]

The development of erythropoietin-stimulating agents seemed to offer an alternative to transfusion for correcting anaemia.[58] In 2001, the US Gynecologic Oncology Group launched a randomised controlled trial of radiotherapy and chemotherapy with or without an erythropoietin-stimulating agent for patients with locally advanced cervical cancer. This trial closed early because of concern of an increased risk of VTE with the use of erythropoietin-stimulating agents. Analyses showed the incidence of VTE was 7·6% in the control group versus 19% in the erythropoietin-stimulating agent group, although this difference was not significant.[3] Other studies that used erythropoietin-stimulating agents in the treatment of cervical cancer have shown VTE incidences that range between 13% and 34% (table 3).[3,51,52,59–61] Three of these studies collected data in a prospective manner.[3,59,61] Furthermore, two randomised controlled trials involving other cancer types also suggested worse outcomes for patients who received erythropoietin-stimulating agents,[62,63] and controversy now exists on the role of erythropoietin-stimulating agents in cancer. Possible mechanisms for the unfavourable effects of erythropoietin-stimulating agents have been postulated, including the presence of erythropoietin receptors on tumour cells,[64] but such mechanisms continue to be investigated. Hypoxia remains a target for curative treatment in cervical cancer, but mechanisms other than increasing haemoglobin with erythropoietin-stimulating agents need to be considered.

Antiangiogenic drugs are another new class of drugs under active investigation for the treatment of cancer. The incidence of VTE in association with the use of these drugs in cervical cancer is not known; however, increased VTE with bevacizumab has been reported with other cancer types.[4] Mechanisms for this side-effect are not well understood and, although bevacizumab has reported activity in cervical cancer,[65] it has not been widely studied in this setting. A search of the US National Cancer Institute Physician Data Query database shows four ongoing trials of antiangiogenic drugs in cervical cancer in both the primary and metastatic setting. The therapeutic ratio of these drugs is yet to be determined.

Outcome

The increase in mortality in the setting of VTE is widely believed to be not only due to VTE itself, but also to worse

	Patients, n	Study design	Treatment	Prophylaxis	Incidence of VTE, n (%)
Thomas et al[3]	109	RCT	Chemoradiotherapy with or without ESA depending on year	None	With ESA: 11/57 (19)
Temkin et al[51]	68	Single-institution retrospective review	Chemoradiotherapy with or without ESA depending on year	NA	With ESA: 4/16 (25)
Wun et al[52]	147	Single-institution retrospective review	Chemoradiotherapy with or without ESA depending on year	None	With ESA: DVT=17/75 (23)
Dusenbery et al[59]	15	Phase I/II single institution study	LND followed by extended-field radiotherapy with or without chemotherapy and ESA	NA	DVT=4 (27)
Lin et al[60]	56 (cervical, vulvar, or vaginal cancer)	Single-institution retrospective review	Chemoradiotherapy and ESA	Coumadin in 24 patients	Without coumadin: 10/32 (31); With coumadin: 9/24 (38); Overall: 34%
Lavey et al[61]	53	Single-arm phase II study	Chemoradiotherapy and ESA	NA	DVT=7 (13)

RCT=randomised controlled trial. ESA=erythropoietin-stimulating agent. NA=not available. OR=odds ratio. LND=lymph=node dissection.

Table 3: **Incidence of VTE in patients with cervical cancer treated with radiotherapy and erythropoietin-stimulating agent**

cancer outcomes.[1,2] In a study by Morgan and colleagues,[2] which involved 74 patients with a gynaecological cancer (28% with cervical cancer), VTE was associated with a two-times increase in the risk of death when controlling for other known prognostic factors. Considerable data exists to suggest that activation of the coagulation cascade promotes angiogenesis and metastases.[7,18,24,66,67] To our knowledge, none of the inter-relations between the coagulation cascade and angiogenesis has been specifically studied in cervical cancer.

Prevention of VTE and treatment

A review of the trials on VTE prevention in the setting of gynaecological cancer surgery highlights the paucity of data on this topic and calls for randomised controlled trials to be done in this patient population.[68] Guidelines from the American College of Chest Physicians (ACCP) also note that very few randomised controlled trials of prophylaxis in the gynaecology–oncology population have been completed in the past decade. Higher doses of unfractionated heparin or low-molecular-weight heparin (LMWH) seem to be needed during gynaecological cancer surgery compared with other surgical settings.[69] Reasons for this need are not known, but might be related to the nature of the surgical procedures or the cancer diagnoses themselves. The ACCP recommends a dose of 5000 IU unfractionated heparin three times a day or a higher dose for LMWH[69] in this setting. No specific recommendations exist for radical hysterectomy for cervical cancer. Similarly, no guidelines have been produced for routine VTE prophylaxis in the setting of brachytherapy. However, because of the concern of an increased risk of VTE during such treatment, most radiation oncologists use VTE prophylaxis routinely for this procedure.

Guidelines for VTE prophylaxis are also absent in the non-surgical setting, and further investigation is needed to define a high-risk group in the cervical-cancer population and to assess the role of prophylactic anticoagulation in this group.

ACCP guidelines for the treatment of VTE in cancer recommend the use of LMWH, which has been shown to be better than coumadin. Treatment should continue for at least 6 months or for as long as the cancer is active.[70] No specific or different recommendations for cervical cancer have been made.

Anticoagulation and survival

The known association between VTE and poor outcome from cancer suggests that primary or secondary prevention of VTE might also affect outcome. Although some improvement in outcome might result from fewer VTE events, experimental evidence suggests that anticoagulation can also inhibit the development of metastases.[71] A randomised trial of LMWH versus unfractionated heparin for prophylaxis of VTE in patients who underwent gynaecological cancer surgery showed an improved survival in patients who received LMWH.[72] Furthermore, an open randomised controlled trial of an non-steroidal anti-inflammatory drug (oxyphenbutazone) in patients with cervical cancer undergoing curative radiotherapy noted improved survival in those assigned oxyphenbutazone.[73] Similarly, more recent and well known trials have shown improved survival with prophylactic or therapeutic LMWH.[74–76] Although none of these studies were done in the exclusive setting of cervical cancer, patients with cervical cancer were included as a small proportion of the total patients enrolled. Therefore, one would expect that their results are able to be generalised to the cervical-cancer population.

Conclusion

Cervical cancer is a common problem worldwide, especially in developing countries, and VTE is a common problem in cervical cancer. We recommend that physicians are diligent in the identification and treatment of VTE in view of what is known about its risk in cervical cancer and its associated risk with surgery, chemotherapy, and radiotherapy. However, accurate reporting of VTE is

Search strategy and selection criteria

Searches of Medline and Embase were done using the terms "uterine cervical neoplasm" and "thromboembolism", and a search of the Cochrane Central database was done using the terms "neoplasm", "cancer", and "thromboembolism". After screening of references in appropriate articles, a further search was done in Pubmed using the terms "tissue factor", "cancer procoagulant", "thrombin", "deep vein thrombosis", and "pulmonary embolism" in conjuction with "cervical cancer", as well as "radical hysterectomy", "deep vein thrombosis", "chemotherapy", and "laparoscopic radical hysterectomy". Articles were restricted to those written in English and published between 1980 and 2006.

clearly a problem in the published work on cervical cancer, and better information on optimum prophylaxis in the surgical setting is needed. Identifying non-surgical patients at high risk who might benefit from prophylaxis also needs further investigation. All studies, especially those on newer drugs auch as antiangiogenics, should accurately document VTE events and report them separately from other cardiovascular events. The combination of these efforts will ensure that the side-effects of existing treatments are properly managed and that new treatments are developed safely, thus optimising the therapeutic ratio.

Conflicts of interest

The authors declared no conflicts of interest.

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