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CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guideline of venous thromboembolism (VTE) and cancer (2019)

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Abstract
In 2011, the Spanish Society of Medical Oncology (SEOM) first published a clinical guideline of venous thromboembolism (VTE) and cancer. This guideline was updated in 2014, and since then, multiple studies and clinical trials have changed the landscape of the treatment and prophylaxis of VTE in cancer patients. To incorporate the most recent evidence, including data from direct oral anticoagulants (DOACs) randomized clinical trials, SEOM presents a new update of the guideline.

Keywords Venous thromboembolism · Cancer · Anticoagulation · Guideline · Low-molecular-weight heparins · Direct oral anticoagulants

Introduction

Cancer and venous thromboembolism (VTE) are two events that walk together [1]. Cancer patients have a four-to-sevenfold increased risk of VTE, being the second cause of preventable death in cancer patients. Therefore, the risk of suffering a severe hemorrhage is doubled when patients are on anticoagulation [2]. There are multiple factors contributing to increase that risk related to specific characteristics of the patient, tumor, and treatments. Moreover, VTE survival in cancer patients is shortened when we compared with similar non-oncologic patients. In recent years, new data have

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appeared on the pathophysiological relationship between cancer and thrombosis and the number of studies targeting specifically this population has increased. Although to date, the standard treatment for VTE in cancer is low-molecular-weight heparins (LMWH), studies with new anticoagulants open new horizons of research and could increase the therapeutic armamentarium for cancer patients with VTE. In this update of the SEOM guidelines to thrombosis and cancer, these data and their respective levels of evidence are reviewed as a useful tool for clinicians.

Methodology

SEOM guidelines have been developed with the consensus of ten oncologists from the Spanish Society of Medical Oncology (SEOM) and Cancer and Thrombosis Section. To assess the level and quality of evidence and to establish a grade of recommendation of the different statements in this guideline, we based ourselves on The Infectious Diseases Society of America-US Public Health Service Grading System (Table 1). The final text was reviewed and approved by all the authors. The goal of this document consists of providing clear practical recommendations about the management of VTE.

Prophylaxis

Prophylaxis of VTE in hospitalized medical cancer patients

Hospitalization is an important VTE-risk factor. Three large randomized phase III trials [3–5] reported a significant reduction in VTE following treatment with LMWH or fondaparinux compared with placebo, but none of them specifically in hospitalized cancer patients. The only evidence available is the subgroup analysis of the aforementioned trials and no major bleeding rates were reported (Table 2). Carrier et al. recently published a meta-analysis of the cancer subgroup of the three randomized clinical trials with contradictory results, showing no significant reduction in the incidence of VTE in cancer patients treated with prophylaxis [relative risk (RR) 0.91; 95% confidence interval (CI) 95% 0.21 to 4.0] [6]. This result was mainly driven by the ARTEMIS clinical trial, with an incidence rate of 17.0% of VTE with fondaparinux versus 3.0% with placebo. This higher incidence of VTE in the prophylaxis arm has not been well understood. Other reasons that could explain this result are the low number of patients included in the meta-analysis (overall 307 patients) and different VTE-risk cancer populations. These contradictory results highlight the lack of conclusive studies. Thus, randomized studies should be designed in this setting with a higher number of patients, and stratifications according to VTE risk and LMWH dose adjustment to obtain definitive conclusions.

Regarding thromboprophylaxis in surgical cancer patients, to extend thromboprophylaxis beyond hospitalization should be considered a matter of importance; however, there is no evidence yet to make this recommendation.

Finally, no specific trials have been performed with direct oral anticoagulants (DOACS) in this setting.

Recommendations

Although data from hospital populations in general cannot be directly extrapolated to cancer patients, in the absence of specific randomized studies for this population, anticoagulation should be considered in the case of hospitalized cancer patients with acute medical illness in the absence of

Table 1 The Infectious Diseases Society of America-US Public Health Service Grading System

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

From [11]

Table 2 Clinical trials assessing prophylaxis of VTE in hospitalized medical patients

Clinical trial	Number of patients	Cancer patients (%)	Study drugs	VTE events	Relative risk reduction	Major bleeding	NNT	Cancer subgroup VTE events
ARTEMIS [3]	849	15.4	Fondaparinux sc (2.5 mg/24 h) vs. placebo	5.6 vs. 10.5% $p=0.029$	0.47	0.2 vs. 0.2% $p=$NS	20	17.0 vs. 3.9%, RR 4.3 NNH 8
MEDENOX [4]	866	12.4	Enoxaparin sc (40 mg/24 h) vs. placebo	5.5 vs. 14.9% $p<0.001$	0.37	1.7 vs. 1.1% $p=$NS	11	9.7 vs. 19.5%, RR 0.50 NNT 10
PREVENT [4]	3706	5.1	Dalteparin sc (5000 UI/24 h) vs. placebo	2.8 vs. 5.0% $p=0.0015$	0.55	0.5 vs. 0.2% $p=$NS	45	3.1 vs. 8.3%, RR 0.37 NNT 18

sc subcutaneously, *VTE* venous thromboembolism, *NS* not significant, *NTT* number of patients needed to treat to avoid one event, *NNH* number needed to harm, *RR* relative risk

contraindications. The preferred agents are LMWH (level of evidence: grade 1B).

Prophylaxis of VTE in surgical cancer patients

VTE is a common complication in cancer patients undergoing surgery, with a twofold or greater increased risk of DVT and four times more risk of a fatal postoperative PE compared to non-cancer population. VTE becomes the cause of a 10% postoperative early mortality rate.

The risk of VTE depends on specific factors of the patient, the tumor and the surgical procedure, the type and duration of the anesthesia, the advanced age of the subject, the residual disease after surgery, obesity, advanced stages of disease, prolonged immobility (more than 3 days), and the most important: background thromboembolism [7, 8].

Several randomized studies and meta-analysis have demonstrated the benefit of pharmacologic prophylaxis with LMWH and UFH over no prophylaxis or placebo unless there is a contraindication [9].

Pharmacological prophylaxis should be started preoperatively, and mechanical methods can be added to increase efficacy [10]. Mechanical methods should not be used as the sole treatment strategy unless there are contraindications for pharmacological prophylaxis (active bleeding or high-risk bleeding).

Classically in clinical practice, prophylaxis is continued for at least 7–10 days. Considering that 40% of VTE events may occur later than 21 days from the surgical intervention [11] and more than 50% after hospital discharge [12], multiple randomized clinical trials and meta-analysis have assessed the benefit of extended thromboprophylaxis in high-risk patients [13, 14]. Bergqvist et al. [15] reported the results of a double-blind trial that enrolled patients undergoing curative surgery for abdominal or pelvic cancer. Patients received 40 mg of enoxaparin daily for 6–10 days, randomized to receive either enoxaparin or placebo for another 21 days. The primary endpoint was the incidence of VTE between days 25 and 31. The incidence of VTE was 4.8% among patients treated with enoxaparin compared with 12.0% treated with placebo ($p=0.02$). This difference was maintained after 3 months with a similar rate of bleeding between groups (5.5% vs. 13.8%). In 2016, Fagarasanu et al. [14] published a systematic review and meta-analysis that included seven randomized and prospective studies comprising 4807 patients. Extended thromboprophylaxis decreased the incidence of all VTE (RR 0.44, 95% CI 0.28–0.70) without significant difference in the incidence of major bleeding (RR 1.19, 95% CI 0.47–2.97). The update of the Cochrane review [13] concludes that prolonged thromboprophylaxis with LMWH significantly reduces the risk of VTE compared to thromboprophylaxis during hospital admittance without increasing bleeding complications or mortality.

The only trial that has assessed the benefit of extended thromboprophylaxis in laparoscopic surgery was published by Vedovati et al. [16]. Two hundred and twenty-five patients that underwent laparoscopic surgery for colorectal cancer were randomized to 1 week or 4 weeks of thromboprophylaxis with LMWH. VTE incidence rate at 4 weeks after surgery was 9.7% in the 1-week arm compared to 0% in the extended treatment arm ($p=0.001$), with a similar incidence of bleeding and mortality rates. Similar efficacy results were observed at 3 months (VTE incidence 9.7% vs. 0.9%; $p=0.005$).

Recommendations

In the absence of contraindications, all patients undergoing major surgical intervention should receive pharmacologic thromboprophylaxis (level of evidence: grade 1A). The preferred agents are LMWH and prophylaxis should be started before surgery or as soon as possible in the postoperative period. Mechanical methods may be added to pharmacologic prophylaxis in high-risk patients, but should not be used as

monotherapy, unless pharmacologic prophylaxis is contraindicated (level of evidence: grade 2C). Patients should receive at least 7–10 days of prophylaxis and patients undergoing major abdominal or pelvic cancer surgery with high-risk features should be considered for extended thromboprophylaxis for 4 weeks (level of evidence: grade 1A). We suggest the same recommendations for laparoscopic surgery; risk factors and the duration and type of the procedure must be assessed (level of evidence: grade 2C).

Prophylaxis of VTE in ambulatory cancer patients during systemic therapy

Chemotherapy, hormonotherapy, and different biological and supportive care drugs have been identified as an independent risk factor for VTE. Incidence of thrombosis in these patients varies widely, so it is important to identify patients at higher risk of developing VTE whom prophylaxis may be beneficial. Recently, VTE incidence over 30% have been described in pancreatic cancer [17, 18] and specific molecular subtypes of non-small cell lung cancer (NSCLC) with ROS-1 [19] and ALK rearrangement [20, 21].

Cancer patients are usually unaware of VTE risk [22]. Self-consciousness and education can contribute to identify high-risk patients. In this sense, risk models may be useful to provide them with educational information and warnings.

A recent experience by The Ottawa Regional Cancer Center has used electronic medical records to calculate real-time risks of thrombosis [23]. Out of 580 patients included, 25% were identified as VTE high-risk patients, 11% of which developed VTE. Since many health centers use electronic medical records, the implementation of VTE-risk scores into clinical practice could be a feasible and meaningful measure. Although there is no clear evidence on ratios between them, based on available clinical data, it seems that performing a dynamic assessment and educating cancer patients on VTE risk would improve patients' performance and outcomes.

Khorana score was the first validated risk assessment model (RAM) for identifying VTE high-risk patients receiving chemotherapy. After this publication, different RAM have been published and some of them have been validated (Table 3) [24–32]. Other RAM addressed to specific tumors such as THROLY [33] or testicular germ cell tumors [34].

Different randomized clinical trials and meta-analyses comparing anticoagulant prophylaxis with no intervention or placebo have evaluated the role of primary thromboprophylaxis with LMWH in ambulatory patients receiving anticancer therapy (Table 4) [35–41]. Overall, a significant reduction of 50% in VTE incidence rate was reported across such meta-analyses with LMWH compared with no intervention or placebo [42, 43]. This reduction was higher in patients with pancreatic cancer (82–74%), with an estimated number of patients needed to treat of 11 subjects to prevent one symptomatic VTE event [44], and lung cancer (58%) [34, 45]. Risk of minor bleeding is increased in the LMWH prophylaxis group without significant increase in major bleeding. No significant difference in mortality was reported by any of these studies.

Nowadays, DOACs have broken into clinical practice in cancer patients. Considering VTE prophylaxis, two trials have been recently published in moderate–high-risk ambulatory patients (Table 5). In the AVERT [46], trial apixaban was associated with a significantly lower incidence of VTE in the modified intention-to-treat population but also with a higher incidence of major bleeding episodes. Overall survival was similar in both arms. In contrast, in the CASSINI [47] trial, the incidence of VTE was not lower with rivaroxaban than placebo in the primary intention-to-treat analysis [6% rivaroxaban vs. 8.8% placebo, hazard ratio (HR) 0.66, IC 95% 0.40–1.09; $p = 0.1$]. However, in the per-protocol analysis, the VTE incidence was significantly lower with rivaroxaban than placebo (2.6% vs. 6.4%, HR 0.40, IC 95% 0.20–0.80). No differences in major bleeding or death were observed. Despite both studies used Khorana score ≥ 2 as inclusion criteria, the VTE incidence in the placebo arms was low (10.2–8.8%). Considered together, these trials showed a significant benefit of the oral anticoagulants for the prevention of VTE with an acceptable incidence of major bleeding. Recently, at least two meta-analyses have assessed the role of DOACs in this setting [36, 48]. Beccatini et al. [36] included three randomized clinical trials and describe a significant reduction of VTE with DOACs [odds ratio (OR) 0.49; 95% CI 0.33–0.74]. A similar VTE reduction was also observed in this study with parenteral thromboprophylaxis (OR 0.43; 95% CI 0.33–0.56). The second meta-analysis by Ll et al. showed an RR with DOACs for overall and symptomatic VTE incidence by 6 months of 0.56 (0.35–0.89) and 0.58 (0.29–1.13), respectively. No difference in major bleeding (RR 1.96, 95% CI 0.80–4.82) and clinically relevant non-major bleeding (RR 1.28, 95% CI 0.74–2.20) while on-treatment were observed. When pool together studies of thromboprophylaxis with primary endpoint VTE and survival, VTE was reduced by 50% (OR 0.49, 9 5% CI 0.43–0.61) [36]. There is a lack of data coming from these trials regarding drug interactions; therefore, DOACs are not recommended to be used concomitantly with potent inhibitors or inducers of P-glycoprotein or cytochrome P450 3A4.

Recommendations

Assessment of VTE risk in cancer patients in the outpatient setting is recommended at initiation of systemic therapy and during evolution of treatment and disease. It is recommended to use a validated RAM to assess VTE risk (level of evidence: grade 2C).

Table 3 Risk assessment models

	Khorana score [24]	Vienna CATS score [25]	PROTECHT score [26]	CONKO score [27]	Oncothromb-Tic Onco score extended [28, 29]	Compass-CAT score [30][a]	Onkotev score [31]	Pabinger et al. [32]
Number of variables	5	7	6	6	4	8	8	2
Biomarkers	No	Yes	No	No	Yes	No	No	Yes
Variables								
Type of tumor (very-high-risk tumor/high-risk tumor)	X	X	X	X	X	–	X	X
Anemia (hemoglobin < 10 g/dL) or ESA use	X	X	X	X	–	–	X	–
Leukocytosis (white blood cell count $> 11 \times 10^9$/L)	X	X	X	X	–	–	X	–
Thrombocytosis (platelet count $\geq 350 \times 10^9$/L)	X	X	X	X	–	X	X	–
Body mass index (BMI, kg/m^2)	X BMI > 35	X BMI > 35	X BMI > 35	X BMI > 35	X BMI > 25	–	X BMI > 35	–
D-Dimer > 1.44 g/L	–	X	–	–	–	–	–	X
Soluble P-selectin > 53.1 g/L	–	X	–	–	–	–	–	–
Gemcitabine/platinum-based chemotherapy	–	–	X	–	–	–	–	–
WHO performance status ≥ 2	–	–	–	X	–	–	–	–
Genetic risk score	–	–	–	–	X	–	–	–
Cancer stage	–	–	–	–	X	X	X	–
VTE family history	–	–	–	–	–		–	–
Anthracycline or antihormonal therapy	–	–	–	–	–	X	–	
Time since cancer diagnosis	–	–	–	–	–	X	–	–
Central venous catheter	–	–	–	–	–	X	–	–
Presence of cardiovascular risk factors	–	–	–	–	–	X	–	–
Recent hospitalization for acute medical illness	–	–	–	–	–	X	–	–
Personal history of VTE	–	–	–	–	–	X	X	–

Table 3 (continued)

	Khorana score [24]	Vienna CATS score [25]	PROTECHT score [26]	CONKO score [27]	Oncothromb-Tic Onco score extended [28, 29]	Compass-CAT score [30][a]	Onkotev score [31]	Pabinger et al. [32]
Tumor vascular/ lymphatic compression	–	–	–	–	–	–	X	–
Validation	Yes	–	–	–	Yes	Yes	–	Yes

[a]Limited to breast, colorectal, lung, and ovarian cancers

Routine thromboprophylaxis is not recommended in ambulatory patients with cancer (level of evidence: grade 1B).

Pharmacological thromboprophylaxis with LMWH or DOACs may be considered in high-risk ambulatory cancer patients, as advanced pancreatic cancer, NSCLC with ROS-1 or ALK rearrangement, patients with a Khorana score ≥ 2 or considered high-risk based on a validated RAM, starting of receiving systemic therapy and no contraindications to anticoagulation and low risk of bleeding. There is no consensus about the dose and duration of the thromboprophylaxis; it is suggested at least 12 weeks after the initiation a new systemic therapy. If the choice is thromboprophylaxis with DOACs, a specific drug–drug interaction assessment must be done. It is recommended to discuss with the patient the indication of pharmacological thromboprophylaxis and the potential risk and benefits. Patients who are receiving primary thromboprophylaxis should be closely monitored (level of evidence: grade 1B).

It is recommended to educate patient regarding VTE specifically, including risk factor and early symptoms, at the time of cancer diagnosis and during cancer evolution (level of evidence: 2A).

Prophylaxis of VTE in cancer patients with central venous catheters

Long-term central venous catheters (CVCs) are commonly used in patients with cancer. The placement of a CVC is associated with an increased risk of thrombotic events in upper limbs and pulmonary embolisms (PE). The reported incidence of CVC-associated thrombosis varies widely between studies (0.3–28% symptomatic events and 27–66% asymptomatic events detected by venography) [49]. Different factors may increase the risk of CVC-associated thrombosis, including material, placement technique, location and type of the catheter, tumor characteristics, treatment (chemotherapy, antiangiogenic therapy, hormone therapy, parenteral nutrition, and radiotherapy), and patient factors. Several randomized trials and meta-analyses evaluated the efficacy and safety of (vitamin K antagonists) VKA, UFH, LMWH, and thrombolytics in the prevention of CVC-associated thrombosis. These studies do not support the use of routine thromboprophylaxis for CVC in cancer patients. Several studies [50] including one meta-analysis [51] have suggested that CVC should be placed on the right side, in the jugular vein, and the catheter tip should be positioned at the right atrium/superior vena cava junction.

Recommendations

Routine thromboprophylaxis in cancer patients with CVCs is not recommended (level of evidence: grade 1A).

Catheters should be placed on the right side, in the jugular vein, and the distal tip should be located at the junction of the superior vena cava and the right atrium (level of evidence: grade 1B).

Treatment

The goals of anticoagulant therapy in cancer patients with cancer-associated thrombosis (CAT) are to improve symptoms, reduce risk of recurrent VTE, and decrease the risk of post-thrombotic syndrome (PTS). Anticoagulation is the cornerstone of treatment. Cancer patients present a higher risk of recurrent VTE and anticoagulant treatment-related bleeding compared to those without malignancy during anticoagulation therapy.

Initial treatment of VTE in cancer patients (5–10 days)

Since our previous recommendation of 2014 two Cochrane reviews have been published [52, 53]. Hakoum et al. [52] showed a trend to a decrease in mortality at 3 months (RR 0.66, 95% CI 0.40–1.10) and VTE recurrence (RR 0.69, 95% CI 0.27–1.76) with LMWH compared to unfractionated heparin (UFH). Compared to LMWH or UFH, fondaparinux was not statistically different in all endpoints including mortality, recurrence VTE, and bleeding. In the second meta-analysis [53], a subgroup analysis of cancer patients

Table 4 Randomized clinical trials evaluating primary prophylaxis with LMWH in ambulatory patients receiving systemic anticancer therapy

Study	Number of patients	Type of tumor	Risk of thrombosis based on type of cancer	LMWH, dose, and duration	Primary endpoint	Patient selection based on RAM
PROTECHT [35]	1150	Lung, pancreas, stomach, colorectal, breast, ovarian, head and neck cancer	High (pancreas, stomach) Low (breast, head and neck)	Nadroparin 4 months	Thrombosis-related	No
FRAGEM [36]	123	Pancreas	High	Dalteparin 200 UI/kg/24 h × 4 weeks followed 150 UI/kg/24 h × 8 weeks 12 weeks	Thrombosis-related	No
CONKO-004 [37]	312	Pancreas	High	Enoxaparin 1 mg/kg/24 h × 3 m, followed 40 mg/24 h × 3 m 6 months	Thrombosis-related	No
SAVE ONCO [38]	3212	Lung, colorectal, stomach, pancreas, kidney and ovarian cancer	Moderate–high	Semuloparin 20 mg/24 h Until a change of CT regimen	Thrombosis-related	No
PRODIGE [39]	186 (target sample size 512, stop inclusion due to poor recruitment)	Glioma	High	Dalteparin 5000 IU/24 h 6 months	Thrombosis-related	No
FRAGMATIC [40]	2202	Lung	High	Dalteparin 5000 IU/24 h 24 weeks	Overall survival	No
PHACS [41]	98 (target sample size 404, early terminated due to low recruitment)	All types of tumors	High (pancreatic, gastric) Low (breast)	Dalteparin 5000 IU/24 h 12 weeks	Thrombosis-related	Yes (Khorana score ≥ 3) [b]Screening for VTE required

Study	VTE (%) CT + LMWH vs. CT	Major bleeding CT + LMWH vs. CT	Minor bleeding or other non-major bleeding CT + LMWH vs. CT
PROTECHT [26]	2.0 vs. 3.9%[a] (VTE + ATE); $p = 0.02$	0.7 vs. 0%; $p = 0.18$	7.4 vs. 7.9%; p = NS
FRAGEM [27]	3.4 vs. 23.0%, RR 0.145; $p = 0.002$	3.4 vs. 3.2%	9.0 vs. 3.0%
CONKO-004 [28]	1.2 vs. 9.9%, HR 0.12; $p = 0.001$	4.8 vs. 3.3%, HR 1.4; $p = 1.0$	NR
SAVE ONCO [29]	1.2 vs. 3.4%, HR 0.36; $p < 0.001$	1.2 vs. 1.2, HR 1.05; p = NS	Clinically relevant non-major bleeding 1.6 vs. 0.9, OR 1.86; p = NS Clinically relevant bleeding 2.8 vs. 2.0%, OR 1.41; p = NS
PRODIGE [30]	9.1 vs. 15.0%, HR 0.51; $p = 0.29$	3.0 vs. 0.0%; p = NS (all major bleeds were intracranial)	NR
FRAGMATIC [31]	5.5 vs. 9.7%, HR 0.57; $p = 0.001$	1.1 vs. 0.7; p = NS	Clinically relevant non-major bleeding 4.5 vs. 0.6%
PHACS [32]	12 vs. 21%, HR 0.69; p = NS	2 vs. 2%; p = NS	Minor bleeding 6% vs. 2% Clinically relevant bleeding 14% vs. 2%, HR 7.0; $p < 0.05$

CT chemotherapy, *HR* hazard ratio, *m* months, *mg* milligram, *NS* not significant, *NR* not reported, *RAM* risk assessment model, *sVTE* symptomatic venous thromboembolism, *VTE* venous thromboembolism

[a]Venous thromboembolism incidence plus arterial thromboembolism incidence

[b]Screening for VTE required: compression ultrasonography of the lower extremities and baseline computed tomography of the chest to rule out existing VTE prior to randomization (8.5% had VTE on baseline screening and were not randomized)

Table 5 Prophylaxis of VTE in ambulatory cancer patients during systemic therapy: DOACs' phase III clinical trials

Study	Number of patients	Tumor type	Risk of thrombosis based on cancer types	DOAC, dose, and duration	Primary endpoint	Patient selection based on RAM
AVERT [46]	574 (only chemotherapy)	All types of tumors, including brain tumors Most common tumor: Lymphoma, gynecologic and pancreatic cancer	High (pancreatic, gastric) Low (breast)	Apixaban 2.5 mg/12 h, 6 months	Thrombosis-related, mITT analysis	Yes Khorana score ≥ 2
CASSINI [47]	841 (systemic antineoplastic therapy)	All types of tumors[a] Most common tumor: Pancreatic, gastroesophageal and lung cancer	High (pancreatic, gastric) Low (prostate, testicular)	Rivaroxaban 10 mg/24 h, 6 months	Thrombosis-related, ITT analysis	Yes Khorana score ≥ 2

Study	Screening prior to randomization (entry criterion)	Screening during study	VTE (%) DOACs vs. placebo	Major bleeding (%) DOACs vs. placebo	Mortality (%) DOACs vs. placebo
AVERT	No	No	mITT analysis 4.2 vs. 10.2%, HR 0.41, 95% CI 0.26–0.65; $p < 0.001$	mITT analysis 3.5 vs. 1.8%, HR 2.00, 95% CI 1.01–3.95; $p = 0.046$ Treatment-period analysis 2.1 vs. 1.1%, HR 1.89, 95% CI 0.39–9.24; $p =$ NS CRNM 7.3 vs. 5.5%, HR 1.28, 95% CI 0.89–1.84; $p =$ NR	Death from any cause 12.2 vs. 9.8%, HR 1.29, 95% CI 0.98–1.71; $p =$ NR
CASSINI	Yes Venous compression duplex ultrasonography of both legs	Yes, Compression ultrasonography of both legs at weeks 8, 16 and 24	ITT analysis (primary endpoint) 6.0 vs. 8.8%, HR 0.66, 95% CI 0.40–1.09; $p = 0.10$ Intervention-period analysis 2.6 vs. 6.4%; HR 0.40, 95% CI 0.20–0.80	Intervention-period analysis 2.0 vs. 1.0%, HR 1.96, 95% CI 0.59–6.49 CRNM 2.72 vs. 1.98%, HR 1.34, 95% CI 0.54–3.32; $p = 0.53$	All-cause mortality 20.0 vs. 23.8%, HR, 0.83, 95% CI, 0.62–1.11; $p = 0.213$

CRNM clinically relevant non-major, *HR* hazard ratio, *ITT* intention-to-treat, *mITT* modified intention-to-treat, *NR* not reported, *VTE* venous thromboembolism

[a]Exclusion criteria: diagnosis of primary brain tumors or known history of brain metastases

reported a significant reduction in mortality with LMWH compared to UFH (OR 0.53, 95% CI 0.33–0.85; $p = 0.009$). In the SELECT-D trial, upfront treatment with rivaroxaban showed similar efficacy compared to LMWH [54].

Rivaroxaban can be used as initial treatment of CAT if low risk of bleeding and in the absence of significant drug interactions (level of evidence: grade 1B).

UFH and fondaparinux can be considered alternative agents to LMWH or DOACs (level of evidence: grade 1B).

Recommendations

LMWH at a body weight-adjusted dose is the drug of choice for the initial treatment of CAT (level of evidence: grade 1B).

Table 6 Treatment of CAT: update of randomized clinical trials

Study	Number of patients	Drug, dose, and duration	Primary endpoint	Recurrent VTE	Major bleeding and other bleedings	Mortality
CATCH trial [57]	900	Tinzaparin 175 IU/24 h vs. warfarin at a dose adjusted to maintain the INR within the therapeutic range (2.0–3.0) for a total of 6 months	Recurrent VTE	7.2% vs. 10.5%, HR 0.65, 95% IC 0.41–1.03; $p=0.07$	Major bleeding 2.7 vs. 2.4%, HR 0.89, 95% CI 0.40–1.99; $p=0.77$ CRNMB 10.9 vs. 15.3%, HR 0.58, 95% CI 0.40–0.84; $p=0.004$	33.4 vs. 30.6%, HR 1.08, 95% CI, 0.85–1.36; $p=0.54$
HOKUSAI cancer VTE trial [55]	1050	Edoxaban 30–60 mg vs. dalteparin (CLOT regimen) 6–12 months	Composite of recurrent VTE or major bleeding during the 12 months after randomization regardless of treatment duration Primary endpoint results Edoxaban 12.8% vs. dalteparin 13.5%, HR 0.97, 95% CI 0.70–1.36; $p=0.006$ for non-inferiority	7.9 vs. 11.3%, HR 0.71, 95% CI 0.48–1.06; $p=0.09$ 6 months analysis 6.5 vs. 8.8%, HR 0.75, 95% CI 0.48–1.17; $p=0.21$	Major bleeding 6.9 vs. 4.0%, HR 1.77 (95% CI 1.03–3.04); $p=0.04$ CRNMB 14.6 vs. 11.1%, HR 1.38, 95% CI 0.98–1.94; $p=$ NR Major bleeding and CRNMB 18.6 vs. 13.9%, HR 1.40, 95% CI 1.03–1.89; $p=$ NR 6 month analysis major bleeding 5.6 vs. 3.2%, HR 1.74, 95% CI 0.95–3.18; $p=0.07$	39.5 vs. 36.6%, HR 1.12 (95% CI 0.92–1.37); $p=$ NR 6 month analysis 26.8 vs. 24.2%, HR 1.14, 95% CI 0.90–1.45; $p=$ NR
SELECT-D trial [54] (pilot study)	406	Rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg once daily vs. dalteparin (CLOT regimen) for a total of 6 months	Recurrent VTE	4 vs. 11%, HR 0.43, 95% CI 0.19–0.99; $p=$ NR	Major bleeding 6 vs. 4%, HR 1.83, 95% CI 0.68–4.96; $p=$ NR CRNMB 13 vs. 4%, HR 3.76, 95% CI 1.63–8.69; $p=$ NR	25 vs. 30%, $p=$ NR
ADAM trial [56]	300	Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months vs. dalteparin (CLOT regimen) for a total of 6 months	Major bleeding	3.4 vs. 14.1%, HR 0.26, 95% CI 0.09–0.80; $p=0.018$ Major bleeding plus CRNMB 6.2 vs. 6.3%, HR 0.9, 95% CI 0.41–1.94; $p=0.88$	Major bleeding 0.0% vs. 2.1% dalteparin; $p=0.99$	16% vs. 11%, $p=0.31$

CRNMB Clinically relevant non-major bleeding, *INR* international normalized ratio, *NR* not reported

CLOT regimen: subcutaneous dalteparin at a dose of 200 IU/kg of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU/kg once daily

Long-term treatment of VTE in cancer patients

Since the previous update of the SEOM guideline in 2014, four randomized clinical trials have been presented, three with DOACs [54–56] and one with LMWH [57] (Table 6).

Multiple meta-analyses have shown that LMWH is more effective than VKAs at reducing the risk of recurrent VTE in patients with cancer [58]. The CATCH trial randomized 900 patients with active cancer and compared tinzaparin 175 IU/kg once daily versus warfarin for 6 months. At 6 months, it showed a non-significantly lower incidence of recurrent VTE with tinzaparin (7.2 vs. 10.5%, HR 0.65, 95% CI 0.41–1.03; $p=0.07$). No differences in major bleeding (HR 0.89, 95% CI 0.40–1.99; $p=0.77$) and mortality (HR 1.08, 95% CI 0.85–1.36; $p=0.54$) were observed, though a significant reduction in clinically relevant non-major bleeding (CRNMB) was described in the tinzaparin arm (10.9 vs. 15.3%, HR 0.58, 95% CI 0.40–0.84; $p=0.004$).

HOKUSAI Cancer VTE is the largest trial published to date regarding VTE treatment in cancer patient. It randomized 1050 patients to edoxaban after an initial course of at least 5 days of LMWH or dalteparin based on the CLOT regimen. It was designed as a non-inferiority trial. Edoxaban was administered at a fixed dose of 60 mg daily except in patients with creatinine clearance of 30–50 ml per minute, body weight of 60 kg or less, or in those receiving concomitant treatment with potent P-glycoprotein inhibitors that all received a reduced dose of 30 mg daily. The duration of the study was at least 6 months and up to 12 months. The primary endpoint was a composite of recurrent VTE or major bleeding up to 12 months after randomization. The median drug exposure was higher with edoxaban than dalteparin, 211 vs. 84 days. It should be noted that inconvenience dosing (patient decision) was the reason for permanent study drug discontinuation in 1 in 7 patients in the dalteparin arm compared to 1 in 25 patients in the edoxaban arm. Around one-fourth of the study population met the criteria to received edoxaban 30 mg. All types of cancer were represented in the trial including metastatic or primary brain tumors, and all systemic anticancer therapies were allowed. The primary endpoint was achieved; edoxaban was not inferior to dalteparin for the composite of recurrent VTE and major bleeding (edoxaban 12.8% vs. dalteparin 13.5%, HR 0.97, 95% CI 0.70–1.36; $p=0.006$ for non-inferiority). In the secondary endpoints, a trend to a reduced recurrent VTE was observed for edoxaban (7.9% vs. 11.3%, HR 0.71, 95% CI 0.48–1.06; $p=0.09$) with a significant increase in major bleeding (6.9% vs. 4.0%, HR 1.77, 95% CI 1.03–3.04; $p=0.04$). The most common bleeding location with edoxaban was the gastrointestinal (GI) tract, in particular in the upper GI tract. In addition to genitourinary (GU) bleedings were more frequent with the oral anticoagulation. In a post hoc analysis, Kraaijpoel et al. [59] published later showed that tumors associated with major bleeding were predominantly GI cancers (major bleeding in GI cancers treated with edoxaban 12.5% vs. dalteparin 3.5%, HR 4.0, 95% CI 1.5–10.6, $p=0.005$). The event-free survival and mortality rate were similar in the two arms, and must be pointed out that the main cause of death was cancer related (34.7% in the experimental arm and 32.8% with dalteparin) and only a minority of deaths were VTE related (1.1% with edoxaban and 0.8 in the LMWH arm).

SELECT-D trial is a pilot study that randomized 406 patients to rivaroxaban versus dalteparin (CLOT regimen). Rivaroxaban was administered orally 15 mg twice daily for 3 weeks, then 20 mg once daily up to 6 months. The primary endpoint was VTE recurrence, though no formal hypothesis was established. It was planned a second randomization after 6 months to continue rivaroxaban versus placebo, but it was closed due to poor recruitment based on data and safety monitoring committee recommendation and also the sample size was reduced to 406 patients. After an interim analysis, esophageal and gastric cancer were excluded because of a higher incidence of major bleeding with rivaroxaban compared to LMWH (36% vs. 11%). The VTE recurrence rate at 6 months was significantly lower with rivaroxaban compared to LMWH (4 vs. 11%, HR 0.43 95% CI 0.19–0.99). Again, as observed in the HOKUSAI trial, more major bleeding was described with DOACs compared to subcutaneous treatment (6-month cumulative rate of major bleeding for rivaroxaban 6% vs. 4% for dalteparin, HR 1.83, 95% CI 0.68–4.96). Also, a significant increase in the rate of CRNMB was associated to rivaroxaban (13 vs. 4%, HR 3.76, 95% CI 1.63–8.69). Most major bleeding and CRNMB occurred in the GI and GU tract.

In a recent meta-analysis [60] of these two trials, a non-significant lower incidence of 6-month recurrent VTE was observed (RR 0.65, 95% CI 0.42–1.01) together with a significant increase in the risk of major bleeding (RR 1.74, 95% CI 1.05–2.88) for DOACs in comparison with LMWH. Mortality was comparable in both arms (RR 1.03, 95% CI 0.85–1.26).

The ADAM VTE trial was presented in the 60th American Society of Hematology (ASH) meeting. It randomized 300 patients to apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily or dalteparin (CLOT trial regimen) for 6 months. The primary endpoint was major bleeding. Major bleeding rate was similar in both arms (apixaban 0.0 vs. 2.1% dalteparin; $p=0.99$) and a significant reduction in VTE recurrent rate was described with apixaban (3.4 vs. 14.1%, HR 0.26, 95% CI 0.09–0.80; $p=0.018$). CRNMB was higher with apixaban than LMWH (6.2 vs. 4.2%). The secondary safety composite endpoint, major bleeding plus CRNMB, was comparable in both arms (apixaban 6.2 vs. dalteparin 6.3%, HR 0.9, 95% CI 0.41–1.94; $p=0.88$). The quality of life showed globally better results for apixaban

including concern for excess bruising, stress, irritation, burden of delivery, and overall satisfaction with anticoagulant therapy. The mortality rate at 6 months was similar comparing apixaban with dalteparin (15.9 vs. 10.6%, HR 1.36, 95% CI 0.79–2.35). These results must be taken with caution and must await the final publication and the outcomes of Caravaggio trial [61] (NCT03045406), that will randomize 1168 patients to the same regimens of apixaban and dalteparin used in ADAM trial for 6 months. The primary outcome of the study is objectively confirmed recurrent VTE and this trial will be the largest trial ever performed in CAT treatment setting.

Recommendations

LMWH at a body weight-adjusted dose and DOACs for 6 months are the drugs of choice for long-term treatment of VTE in cancer patients. DOACs must be used in low-risk bleeding patients (increased risk of GI and probably GU bleeding) and with no significant drug–drug interactions (level of evidence: grade 1A).

Extended duration of anticoagulation therapy after 6 months should be considered for high-risk patients such as those with active cancer and those receiving systemic therapy. Beyond 6 months, patients should be re-evaluated frequently to assess the risk–benefit ratio of continuing anticoagulant therapy (level of evidence: grade 2C).

Treatment of CVC-associated thrombosis (CVCAT)

The scientific evidence is scarce. It comes from some retrospective studies [62] and a small prospective study [63] but especially information from lower limb DVT is applied. LMWH is the treatment of choice during 3–6 months and considered indefinite treatment if the catheter is not removed and the cancer is present. The catheter should not be removed [64] unless it is no longer needed, it is infected, there is any contraindication to anticoagulation treatment, or there is no response to it. Removal should be done after 5–7 days of anticoagulant treatment. Related to DOACs, experience in CVCAT is limited [65] and comparison with LMWH is not available, but could be considered with the same nuances than in the rest of VTE.

Recommendations

It is recommended treatment with LMWH during 3–6 months or consider indefinite treatment if CVC is not removed (level of evidence: 2B). DOACs could be considered an option of CVCAT (level of evidence: 2C). We recommend not to remove the catheter unless it is not necessary, infected, anticoagulation treatment is contraindicated, or anticoagulation failure of appropriate therapy (level of evidence 2B).

Treatment of incidental thromboembolic events

Incidental VTE (iVTE) is a growing problem in cancer patients and accounts up to 50% of all VTE events in some retrospective studies, and it is likely to increase further with the improvements of imaging techniques. In the recent randomized clinical trials of DOACs vs. LMWH, incidental VTE events were included [54, 55]. Similar recurrent VTE, bleeding complications, and mortality rates, comparing incidental PE and deep vein thrombosis (DVT) with symptomatic events has been described [66, 67]. However, there is limited evidence about the optimal management of isolated, incidental subsegmental PE and incidental visceral vein thrombosis (iVVT), in particular splanchnic vein thrombosis (SVT) [68]. Some observational retrospective and prospective studies have suggested a similar outcome of incidental subsegmental PE compared to patients with more proximal clots or symptomatic events [67, 69], but the precise role of anticoagulation remains unknown in isolated cases. The available data in SVT or iVVT are even more scarce. Two international registries [70, 71] that included cancer patients (35–45% of the overall population) analyzed the outcomes and prognosis of incidental SVT. The prognosis of incidental SVT was comparable to the symptomatic SVT, and in the multivariable analysis, anticoagulation seemed to reduce the incidence of thrombotic events (HR 0.85, 95% CI 0.76–0.96) without impact in major bleeding risk.

Recommendations

Incidental VTE (PE and DVT) should be treated as symptomatic VTE and anticoagulation therapy with LMWH or DOACs is considered the standard treatment (level of evidence: 1B).

Treatment of isolated, incidental subsegmental PE, or incidental SVT should be individualized in every patient. Despite the low evidence available, it is suggested to consider anticoagulation therapy (level of evidence: 2C).

Treatment of recurrent VTE during anticoagulation therapy

The recurrent rate of VTE on anticoagulation therapy in the most recent randomized trials ranges between 4 and 11%. Type of tumor, stage, active cancer, cancer progression, and prior history of VTE have been found to be risk factors for VTE recurrence. There is a lack of randomize clinical to guide the management of recurrent VTE in cancer patients. An empirical approach for the management of recurrent VTE is proposed. First of all, in the setting of a recurrent

event, doses and treatment compliance should be checked and also the absence of heparin induced thrombocytopenia (HIT) ruled out. Patient receiving VKA while the recurrence is diagnosed should switch to LWMH or DOACs. However, currently, the majority of cancer patients with VTE are treated with LWMH. If recurrent VTE occurs while infra-therapeutic LMWH, it is recommended to increase to therapeutic dose or switch to DOACs. If therapeutic dose of LMWH is being used, two retrospective cohort studies [72, 73] support the use of 25% dose escalation of LWMH. Even a small number of patients with another recurrent event despite dose escalation were managed successfully using further dose escalation. Monitoring anti-Xa levels to guide dose escalation could be considered, but the association between clinical efficacy of LMWH and anti-Xa levels is not completely probed. Alternatively, a switch to DOACs could be proposed based on the lower recurrent rate compared to LMWH described in the randomized clinical trials HOKUSAI, SELECT-D, and ADAM. Probably, the number of patients treated with DOACs will increase in the near future, and if recurrence VTE occurs, it is recommended to switch to LMWH based on expert opinions. Vena cava filters have been associated to an increased long-term risk of VTE and no impact in short- or long-term survival has been proved with its used [74–76]. Use of vena cava filter only could be justified if anticoagulant therapy is contraindicated or further recurrences occur despite proper anticoagulation is administered. Due to the uncertain benefit of vena cava filter insertion a retrievable filter is preferred and anticoagulant therapy should be resumed as soon as possible.

Recommendations

It is suggested that if recurrence occurs on VKA or prophylactic or intermediate doses of LMWH, therapeutic doses of LMWH or switch to DOACs should be initiated (level of evidence: grade 2B).

If recurrence occurs on therapeutic doses of LMWH, a 25% dose escalation should be considered or a switch to DOACs (level of evidence: grade 2B).

If recurrence occurs while treatment with DOACs switch to LMWH should be considered or alternatively DOACs dose escalation if infra-therapeutic dose was used (level of evidence: grade 3C).

Vena cava filter insertion may be considered if anticoagulation is contraindicated or further recurrent events occur despite appropriate anticoagulant therapy (failure of anticoagulation). Insertion of vena cava filter is associated with a lack of survival benefit and increased risk of long-term VTE. It is preferred a retrievable filter and anticoagulation should be resumed as soon as possible (level of evidence: grade 2B).

VTE treatment of central nervous system (CNS) primary tumors and metastasis

Since there are not specific trials for brain tumors, general rules for anticoagulation in CAT should be applied to these cases. However, some clinical data are available.

In a retrospective study with 182 patients with primary or metastatic brain tumors and 182 with other tumors with CAT, median duration of anticoagulation was 6.7 months [77]. No differences in the incidence of recurrence (11.0 vs. 13.5 cases per 100 patients-year, $p = 0.26$) or major bleeding (8.9 vs. 6.0 cases per 100 patients-year, $p = 0.80$) were observed.

At a second retrospective study with 293 patients with brain metastases, 104 patients with VTE were treated with enoxaparin [78]. No differences in intracranial bleeding were described for treated or not treated groups (44 vs. 37%, $p = 0.13$). Nevertheless, the incidence of hemorrhage was significantly higher for patients with melanoma or renal cancer, although not related to heparin used.

A recent meta-analysis including 1480 patients with neoplastic cerebral involvement studied the incidence of intracranial bleeding between anticoagulated and not patients [79]. The OR obtained were: 2.13 (95% CI 1.0–4.56) for all patients; 1.07 (95% CI, 0.61–1.88) for metastatic patients; and 3.75 (95% CI 1.42–9.95) for patients with glioma. Interestingly, the incidence of hemorrhage was not due to use of low-molecular weight heparin (OR 0.75, 95% CI 0.24–2.33).

A retrospective cohort study showed that DOACs are not associated with an increased incidence of intracranial bleeding compared to LMWH in patients with brain metastases or primary brain tumors.

Recommendations

In absence of contraindications, same recommendations for management of CAT as in other solid tumors should be applied for patients with primary or metastatic CNS tumors (level of evidence: grade 2B).

For patients with brain metastases from melanoma or kidney cancer, due to a greater risk of bleeding, a 25–50% reduction of LMWH dose may be considered (level of evidence: grade 2C).

For patients with brainstem glioma, due to potential severity of bleeding, a 25–50% reduction of LMWH is suggested (level of evidence: grade 2C).

Anticoagulation in the absence of VTE to improve survival in cancer patients

The existence of a relation between pathophysiological pathways of the hemostatic system and cancer development and progression has been confirmed by several preclinical research studies [80]. Hemostatic system activation would favor tumor transformation and progression, throughout angiogenesis, increasing local invasion and remote metastasis dissemination and growth. Quite relevant are: tissue factor, thrombin, and activated protease receptors. Tumor growth and metastatic process require a fibrin matrix as well as selectins, both implied in metastatic growth. Coagulation inhibition with anticlotting treatments might also play an antitumor role beyond antithrombotic effects. Preclinical studies have demonstrated that LMWH might inhibit or slow down tumor growth while binding to cell membrane selectins, inducing angiogenesis blockade, growth factors, and cell signaling inhibition which difficult extracellular tumor matrix formation [81].

Different clinical trials designed to study the prevention role of anticlotting treatments in the progression or relapse of VTE in cancer patients, which confirmed a potential survival benefit, larger than the one expected from VTE-risk reduction [82].

Several studies, comprising different patients and treatments, conducted to see the effect of LMWH (study primary end point) on global survival in the absence of VTE have shown contradictory results, in some cases statistically significant in subsets of patients with non-metastatic diseases, of a better prognosis, which triggered the hypothesis that they would benefit the most from adding LMWH to a standard treatment [83, 84].

In recent years, several studies have been published, focused on tumors with a high thrombotic potential, as lung cancer. These studies have shown no survival benefit from adding LMWH to ambulatory treatments or they have given uneven results. ABEL clinical trial evidenced a significant enhancement of the progression-free survival (HR 2.58) and overall survival (HR 2.96) by adding bemiparin to chemotherapy for treating small cell lung cancer patients with limited disease [85]. Other similar purpose studies conducted in lung cancer patients with different histological subtypes, including a bigger number of patients, have not confirmed any significant survival benefit from adding LMWH [40, 86].

Recent evidence analysis by Kahale et al. [87] could not confirm any survival benefit from treatments with oral anticoagulant agents, VKA, or DOACs in cancer patients with no previous VTE, but they did confirm an increase of bleeding risk.

Recently, it has been suggested that the determination of biomarkers related to the coagulation cascade activation and tumor progression would favor a correct selection of those patients that will benefit from anticoagulant treatments for enhancing survival [88].

Recommendation

Anticlotting treatment in cancer patients should not be prescribed with the purpose of enhancing survival, unless studied within the context of clinical trials (evidence level 1B).

Compliance with ethical standards

Conflict of interest AMM reports consulting or advisory role from Celgene, Sanofi, Pfizer, Bristol-Myers Squibb, LEO Pharma, Daiichi Sankyo, Bayer and Halozyme; Speakers' Bureau from Rovi; Research Funding from Sanofi and LEO Pharma; Travel, Accommodations, Expenses from Celgene, Roche and Merck Serono. Patents, Royalties, Other Intellectual Property: Risk assessment model in venous thromboembolism in patients with cancer. EG reports from the work under consideration for publication Consultant or advisory role from Rovi, Daiichi Sankyo, Techdow, Sanofi, Pfizer and BMS. Speakers' Bureau from Rovi, Daiichi Sankyo, Leo Pharma and Sanofi. Travel, Accommodations and Expenses from Rovi, Daiichi Sankyo and Leo Pharma. Relevant financial activities outside the submitted work: Consultant or Advisory Role from Bayer, Merck, Ipsen, Novartis, Eisai, EUSA Pharma, Roche, Janssen, Astellas and AstraZeneca. Speakers' Bureau from Bayer, Pfizer, BMS, Ipsen, Novartis, Eisai, Roche, Astellas, Janssen, Menarini and MSD. Travel, Accommodations and Expenses from Pfizer, Bayer, Ipsen, Roche, Novartis, Eisai, BMS, Pierre Fabre, Astellas, Janssen and Sanofi. Grant support (personal/institutional) from Pfizer, Bayer, Ipsen, Roche, BMS, Astellas, Janssen, Sanofi, Ferrer. IGE reports from the work under consideration for publication, Consultant or Advisory Role from Rovi. Speakers' Bureau from Rovi and Leo Pharma. Travel, Accommodations and Expenses from Rovi and Leo Pharma. Relevant financial activities outside the submitted work: Travel, Accommodations and Expenses from Roche and Sanofi. RMM has nothing to disclose. VM has nothing to disclose. VPO reports speaker honoraria from Rovi, Leo Pharma and Sanofi; Advisory from daiichi sankyo. PPS reports speaker honoraria from Leo pharma. TQV reports Consulting or Advisory Role from Novartis and Glaxo-Tesaro; Speakers' Bureau from Rovi, Sanofi, Roche and Pfizer; Travel, Accommodations and Expenses from Roche. MS reports Consultant or Advisory Role from Rovi; Speakers' Bureau from Rovi and Leo Pharma. Travel, Accommodations and Expenses from Rovi and Leo Pharma. Relevant financial activities outside the submitted work: Consultant or Advisory Role from Merck, Amgen and Celgene; Speakers' Bureau from Celgene, Servier and Amgen. Travel, Accommodations and Expenses from Roche and Servier. Grant support (personal/institutional) from Mylan and Kern Pharma.

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Informed consent Inform consent is not needed.

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