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Direct Oral Anticoagulants for the Treatment of Cancer-Associated Venous Thromboembolism: A Latin American Perspective

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Abstract

Venous thromboembolism (VTE) is a leading cause of morbidity and mortality in patients with cancer. On the basis of results from randomized controlled trials, direct oral anticoagulants (DOACs) are now recommended for the treatment of cancer-associated VTE. The decision to use a DOAC requires consideration of bleeding risk, particularly in patients with gastrointestinal (GI) malignancies, the cost-benefit and convenience of oral therapy, and patient preference. While efficacy with apixaban, edoxaban, and rivaroxaban versus dalteparin has been consistent in the treatment of cancer-associated VTE, heterogeneity is evident with respect to major GI bleeding, with an increased risk with edoxaban and rivaroxaban but not apixaban. Although cost and accessibility vary in different countries of Latin America, DOACs should be considered for the long-term treatment of cancer-associated VTE in all patients who are likely to benefit. Apixaban may be the preferred DOAC in patients with GI malignancies and LMWH may be preferred for patients with upper or unresected lower GI tumors. Vitamin K antagonists should only be used for anticoagulation when DOACs and low molecular weight heparin are inaccessible or unsuitable.

Keywords

anticoagulation, cancer, venous thromboembolism

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Introduction

Venous thromboembolism (VTE), comprising deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication and leading cause of morbidity and mortality among patients with cancer.[1–4] While VTE itself may be a direct cause of death in patients with cancer, it is also linked with poor oncologic prognosis.[5] There are limited studies on the epidemiology of cancer-associated VTE in Latin America, but given that both malignancy and cancer treatments induce a hypercoagulable state,[6,7] its incidence is expected to be similar to that in the United States, Canada and European populations, with common cancers, such as breast, lung, colon and prostate cancer, contributing most to the burden of disease.[2,8] Compared with non-cancer patients, patients with cancer have a significantly greater risk of recurrent VTE and bleeding complications during anticoagulant therapy.[9] Case fatality of recurrent VTE in cancer patients is, however, higher than major bleeding case fatality.[10] Given that active cancer is an independent risk factor for both bleeding and recurrent VTE,[11] and the severe consequences of VTE in this population, cancer patients with cancer and VTE should be considered for extended anticoagulation for as long as the cancer is active (ie within 6 months of diagnosis, while on active treatment, or when not in remission), with careful balancing of the risks and benefits of the available treatment options.[12–16]

Based mainly on the results of the small but seminal CLOT study, which showed the low molecular weight heparin (LMWH), dalteparin, to be more effective than and as safe as vitamin K antagonist (VKA) therapy (warfarin with LMWH bridging therapy) for the treatment of VTE in cancer patients,[17] LMWH has historically been the standard of care for the initial and long-term treatment of cancer-associated VTE.[18,19] For patients receiving VKA in the CLOT study, the international normalized ratio was in the therapeutic range only 46% of the time,[17] which may have contributed to the reduction in recurrent VTE seen with LMWH versus VKA, and reflects the difficulty of maintaining therapeutic VKA levels in the cancer setting. In general, randomized controlled trials (RCTs) have shown that LMWH is associated with reduced risk of recurrent VTE versus VKAs in patients with cancer-associated VTE, but RCTs have also shown that LMWH has no advantage with respect to major bleeding or survival in this setting, and that the remaining risk of VTE recurrence is still significant (~7-10%).[17,20,21]

Direct oral anticoagulants (DOACs), which include the direct factor Xa inhibitors apixaban, edoxaban and rivaroxaban, and the direct thrombin inhibitor dabigatran, have been incorporated into the standard of care for the treatment of VTE in the general population.[22] However, until recently, there have been limited RCT data on the efficacy and safety of DOACs in patients with cancer-associated VTE. Data from RCTs of edoxaban or rivaroxaban versus dalteparin have now provided high-level evidence that these DOACs are effective alternatives to LMWH for the treatment of cancer-associated VTE,[23,24] but caution is advised in patients with high bleeding risk, particularly those with upper gastrointestinal (GI) malignancies.[12–16] More recently available RCT evidence also suggests a role for apixaban for the treatment of VTE in patients with cancer, including those with GI lesions.[25,26] There are currently no published RCT results relating to dabigatran for the treatment of cancer-associated VTE.

In Latin American countries, the particularly high pharmacy purchase cost of LMWH and the difficulty of maintaining subcutaneous LMWH injections long-term are major barriers to appropriate anticoagulation for cancer patients diagnosed with VTE.[19,27] Although LMWH is recommended for cancer-associated VTE, it is underutilized and often prematurely discontinued, and low-cost oral VKA therapy may remain a common treatment strategy in some regions.[6,19,27–29] Unlike VKAs, DOACs are administered in fixed doses and do not require laboratory monitoring of the anticoagulant effect, and thereby represent a convenient and potentially cost-effective alternative to both LMWH injections and VKAs for long-term anticoagulation in patients with active cancer and VTE.[19] However, DOACs do have interactions with common drugs used in cancer patients, and care must be taken to assess the potential clinical impact of these interactions.[30,31] Deciding whether to prescribe a DOAC for a patient with cancer is, however, not always straightforward, especially in the presence of factors commonly encountered in cancer patients that further increase bleeding risk but are not well represented in RCTs.[18,31,32] In the absence of equivalent regional or local guidelines, Latin American clinicians tend to rely on guidelines from major American societies such as the American College of Chest Physicians (ACCP), American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH) and National Comprehensive Cancer Network (NCCN) to inform such decisions.[12,16,22,33]

Here, we review the evidence and international guideline recommendations for DOACs in the treatment of cancer-associated VTE. Recommendations based on the most up-to-date high-level evidence are highlighted, and suggestions based on expert opinion and experience are provided for issues commonly encountered in cancer patients that lack adequate clinical trial data to inform evidence-based recommendations.

Evidence for DOACs in the Treatment of Cancer-Associated VTE

Initial evidence supporting the use of DOACs in the treatment of cancer-associated VTE was obtained from the pooled subgroup of patients with cancer (n = 1132; 3-5% of the overall population) included in phase III RCTs conducted in the general population.[34–39] A meta-analysis of the pooled data showed a non-significant reduction in recurrent VTE of approximately 40%, and a non-significant reduction in major bleeding of approximately 30% for DOACs versus VKA + heparin bridging therapy.[40] Patients with active cancer for whom treatment with LMWH would be considered appropriate were, however, often excluded from the studies included in this meta-analysis,

meaning that the studied population was unlikely to be representative of the target cancer patient population, as indicated by the low rates of metastatic disease (10-12%) and VTE recurrence (2-3%) observed in these studies relative to the CLOT study (60% and 12%, respectively).[17,40] Another factor limiting the relevance of these findings is the use of VKA as the comparator treatment rather than the LMWH standard of care for cancer patients.

Results from four RCTs (Hokusai VTE Cancer, SELECT-D, Caravaggio and ADAM VTE) comparing the safety and efficacy of the factor Xa inhibitor DOACs versus the standard CLOT regimen of dalteparin (200 IU/kg for 1 month, followed by 150 IU/kg) for the treatment of cancer-associated VTE have now been published (Table 1).[23–26] These studies recruited a broad spectrum of patients predominantly with active cancer, including elderly patients, patients with incidental VTE as the index event, patients receiving standard concurrent anticancer drug therapies (cytotoxic, hormonal, targeted or immunomodulatory), patients with metastatic disease, and patients with upper or lower GI tumors, with only slight differences in the distribution of cancer types.

Hokusai VTE Cancer

The 12-month Hokusai VTE Cancer trial, was the first RCT of a DOAC for the treatment of cancer-associated VTE.[23] This non-inferiority trial had a composite primary outcome of recurrent VTE or major bleeding episode, akin to a net clinical benefit outcome. Patients included in the trial had acute symptomatic or incidentally detected proximal leg DVT or PE, and active cancer or a diagnosis of cancer within the previous 2 years. Standard once-daily dosing of edoxaban 60 mg was started after ≥5 days of lead-in therapeutic-dose LMWH. Patients with body weight <60 kg, creatinine clearance of 30–50 mL/min, or taking strong P-glycoprotein (P-gp) inhibitors received reduced-dose edoxaban (30 mg once daily). Patients received edoxaban or dalteparin for at least 6 months and up to 12 months.

Despite inclusion criteria allowing for enrollment of patients with a history of cancer as well as patients with active cancer, >97% of patients had active cancer. In addition to antimetabolites (~23% of patients), platinum-based chemotherapy (~20% of patients) and other standard chemotherapy and hormonal anticancer agents, approximately 3% of patients were receiving concomitant therapy with the antiangiogenic monoclonal antibody bevacizumab.

The primary composite outcome occurred in 12.8% of patients in the edoxaban arm and 13.5% patients in the dalteparin arm ($p = 0.006$ for non-inferiority). When the components of the primary outcome were analyzed, there was a trend toward a reduction in recurrent VTE with edoxaban versus dalteparin (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.48-1.06), but there was excess major bleeding with edoxaban (HR 1.77; 95% CI, 1.03-3.04; $p = 0.04$). There was also a trend toward more clinically relevant non-major (CRNM) bleeding with edoxaban versus dalteparin (HR 1.38; 95% CI, 0.98-1.94). The higher rate of major bleeding with edoxaban was mainly accounted for by GI bleeding, particularly upper GI bleeding, in patients with GI cancer. There was a suggestion of slightly more major genitourinary (GU) bleeding with edoxaban (0.4% vs 0 with dalteperin). A post hoc subgroup analysis showed that while there was a significant increase in major bleeding for edoxaban versus dalteparin in patients with GI cancer (12.7% vs 3.6%; HR 4.0; 95% CI, 1.5-1.06; $p = 0.005$), there were no significant differences in non-GI cancer patients, including patients with GU cancers (4.6% vs 2.4%).[41] In patients with GI cancer, upper GI bleeding accounted for 16/21 (71.4%) major bleeding events in the edoxaban group, and in none of the 5 major bleeding events in the dalteparin group.[41] Out of the 16 major upper GI bleeding events in patients with GI cancer receiving edoxaban, 12 (75%) occurred in patients with unresected tumors,[41] suggesting that patients with intact GI tumors had the greatest risk of bleeding with edoxaban.

SELECT-D

The next RCT to evaluate a DOAC for the treatment of cancer-associated VTE was the SELECT-D study.[24] This was a pilot study of rivaroxaban versus dalteparin for the treatment of acute symptomatic leg DVT or symptomatic or incidental PE in patients with active cancer. The primary outcome was VTE recurrence. Standard dose rivaroxaban (15 mg twice daily for 3 weeks then 20 mg once daily) or dalteparin was administered for 6 months.

The results of the SELECT-D trial were consistent with those of the Hokusai VTE Cancer study, in that rivaroxaban reduced the rate of recurrent VTE versus dalteparin, but at the cost of more bleeding. The cumulative rate of VTE recurrence rate at 6 months was 11% for the rivaroxaban treatment group and 4% for the dalteparin group (HR 0.43; 95% CI, 0.19-0.99). SELECT-D was not powered to show a significant difference between rivaroxaban and dalteparin with respect to major bleeding, but there was a trend towards more major bleeding with rivaroxaban (HR 1.83; 95% CI, 0.68-4.96). Most major bleeding events with rivaroxaban were GI bleeds. Patients with esophageal or gastroesophageal cancer tended to have more major bleeds with rivaroxaban (36%) than with dalteparin (11%). Recruitment of patients with cancer of the esophagus or gastroesophageal junction into the study was stopped when the increased risk of major bleeding with rivaroxaban in patients with upper GI tumors became clear. Rivaroxaban was associated with a clear increase in CRNM bleeding (HR 3.76; 95% CI, 1.63-8.69), most of which was GI or GU bleeding.

ADAM VTE

ADAM VTE was a was a small pilot study conducted to compare the safety of apixaban and dalteparin for the treatment of VTE, which included lower or upper extremity DVT or PE, in patients with active cancer.[26] Compared with the other trials, inclusion of patients with upper extremity DVT, small sample

Table 1. Characteristics and efficacy and safety outcomes of randomized trials comparing the safety and efficacy of DOACs (apixaban, edoxaban or rivaroxaban) and dalteparin in the treatment of VTE in patients with cancer.[23–26]

	Caravaggio		ADAM-VTE		Hokusai VTE Cancer		SELECT-D	
	Apixaban (n = 576)	Dalteparin (n = 579)	Apixaban (n = 150)[a]	Dalteparin (n = 150)[b]	Edoxaban (n = 522)	Dalteparin (n = 524)	Rivaroxaban (n = 203)	Dalteparin (N = 203)
Age, mean (SD) or median (range) years	67.2 (11.3)	67.2 (10.9)	64.4 (11.3)	64.0 (10.8)	64.3 (11.0)	63.7 (11.7)	67 (22–87)	67 (34–87)
Male, n (%)	292 (50.7)	276 (47.7)	72 (48.0)	73 (48.7)	277 (53.1)	263 (50.2)	116 (57.1)	98 (48.3)
Active cancer, n (%)	559 (97.0)[c]	565 (97.6)[c]	150 (100)[d]	150 (100)[d]	513 (98.3)[e]	511 (97.5)[e]	203 (100.0)[e]	203 (100.0)[e]
Metastatic disease, n (%)	389 (67.5)[f]	396 (68.4)[f]	96 (64.0)	97 (64.7)	274 (52.5)	280 (53.4)	118 (58.1)	118 (58.1)
Cancer treatment, n (%)	350 (60.8)[g]	367 (63.4)[g]	108 (73.5)	110 (74.3)	374 (71.6)[g]	383 (73.1)[g]	140 (69.0)[h]	142 (70.0)[h]
GI cancers, n (%)	188 (32.6)	187 (32.3)	48 (32.0)	57 (38.0)	165 (31.6)	140 (26.7)	91 (45.0)	86 (42.4)
Colorectal	121 (21.0)	113 (19.5)	18 (12.2)	29 (19.6)	83 (15.9)	79 (15.1)	55 (27.0)	47 (23.0)
Upper GI	23 (4.0)	31 (5.4)	7 (4.8)	4 (2.7)	33 (6.3)	21 (4.0)	15 (7.0)	26 (12.0)
Incidental DVT or PE, n (%)	116 (20.1)	114 (19.7)	NR	NR	167 (32.0)	173 (33.0)	108 (53.2)	105 (51.7)
Recurrent VTE, n (%)	32 (5.6)	46 (7.9)	1 (0.7)	9 (6.3)	41 (7.9)	59 (11.3)	8 (4.0)[i]	18 (11.0)[i]
HR (95% CI); DOAC vs dalteparin	0.63 (0.37–1.07)		0.099 (0.013–0.78)		0.71 (0.48–1.06)		0.43 (0.19–0.99)	
Major bleeding, n (%)	22 (3.8)	23 (4.0)	0	2 (1.4)	36 (6.9)	21 (4.0)	11 (6.0)[i]	6 (4.0)[i]
HR (95% CI); DOAC vs dalteparin	0.82 (0.40–1.69)		0.0 (0.0-)		1.77 (1.03–3.04)		1.83 (3–11)	
Major GI bleeding, n (%)	11 (1.9)	10 (1.7)	0	0	20 (3.8)	6 (1.1)	8 (3.9)	4 (2.0)
HR (95% CI); DOAC vs dalteparin	1.05 (0.44–2.50)		NE		NR		NR	
CRNM bleeding, n (%)	52 (9.0)	35 (6.0)	9 (6.2)	7 (4.2)	76 (14.6)	58 (11.1)	25 (13.0)[i]	7 (4.0)[i]
HR (95% CI); DOAC vs dalteparin	1.42 (0.88–2.30)		NR		1.38 (0.98–1.94)		3.76 (1.63–8.69)	
Mortality, n (%)	135 (23.4)	153 (26.4)	23 (16)	15 (11)	206 (39.5)	192 (36.6)	48 (23.6)	56 (27.6)
HR (95% CI); DOAC vs dalteparin	0.82 (0.62–1.09)		1.40 (0.82–2.43)		1.12 (0.92–1.37)		NR	

CI, confidence interval; CRNM, clinically relevant non-major; DVT, deep vein thrombosis; GI, gastrointestinal; HR, hazard ratio; NE, not evaluated; NR, not reported; DOAC, direct oral anticoagulant; PE, pulmonary embolism; PET, positron emission tomography; SD, standard deviation; VTE, venous thromboembolism.

[a]Primary analysis population (n = 145).

[b]Primary analysis population (n = 142).

[c]Cancer diagnosed within the past 6 months; receiving anticancer treatment at the time of enrollment or within the past 6 months; or recurrent locally advanced or metastatic cancer.

[d]Any evidence of cancer on cross-section or PET imaging; metastatic disease; and/or cancer-related surgery, chemotherapy, or radiation therapy within the past 6 months.

[e]Cancer diagnosed within the past 6 months; recurrent, regionally advanced or metastatic cancer; cancer for which treatment had been administered within the past 6 months; hematologic cancer not in complete remission.

[f]Recurrent locally advanced or metastatic disease.

[g]Any anticancer drug therapy (cytotoxic, hormonal, targeted and/or immunomodulatory), radiotherapy and/or surgery.

[h]Chemotherapy, radiotherapy, targeted therapy and/or hormonal therapy.

[i]Cumulative percentages.

Table 2. Efficacy and safety outcomes of meta-analyses of the Hokusai VTE cancer, SELECT D, ADAM VTE and Caravaggio trials of DOACs versus LMWH for the treatment of cancer-associated VTE.[42,47,48,50–52]

Meta-analysis	Number of patients analyzed	VTE recurrence[a]	Major bleeding[a]	CNRMB[a]
Giustozzi et al.	2894	RR, 0.62; 95% CI, 0.43–0.91	RR, 1.31; 95% CI, 0.83–2.08	RR, 1.51; 95% CI, 1.09–2.09
Haykal, et al.	2907	RR, 0.62; 95% CI, 0.44–0.87	RR, 1.33; 95% CI, 0.45–4.22	RR, 1.58; 95% CI, 1.11–2.24
Moik, et al.	2894	RR, 0.62; 95% CI, 0.43–0.91	RR, 1.31; 95% CI, 0.83–2.08	RR, 1.65; 95% CI, 1.19–2.28
Mulder, et al.[b]	2607	RR, 0.68; 95% CI, 0.39–1.17	RR, 1.36; 95% CI, 0.55–3.35	RR, 1.63; 95% CI, 0.73–3.64
Saleem, et al.	2907	HR, 0.54; 95% CI, 0.23–1.28	HR, 1.38; 95% CI, 0.45–4.22	HR, 1.77; 95% CI, 0.49–6.40
Tao, et al.	2894	HR, 0.62; 95% CI, 0.43–0.91	HR, 1.31; 95% CI, 0.83–2.08	HR, 1.65; 95% CI, 1.19–2.28

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding; HR, hazard ratio; LMWH, low molecular weight heparin; DOACs, direct oral anticoagulants; RR, risk ratio; VTE, venous thromboembolism.
[a]DOACs versus LMWH.
[b]ADAM VTE not included.

size and a slightly different distribution of cancer types (including slightly fewer patients with upper GI malignancy) in ADAM-VTE, may have contributed to a relatively low-risk population, as suggested by overall lower recurrent VTE, major bleeding and mortality rates in the study.[42,43] Patients received standard dose apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) or dalteparin over 6 months.

Compared with dalteparin, apixaban was associated with low rates of bleeding and VTE recurrence. The primary outcome of major bleeding up to 6 months occurred in none of the patients receiving apixaban, and 1.4% of patients receiving dalteparin ($p = 0.14$). The rate of recurrent VTE was significantly lower in the apixaban group than the dalteparin group (HR 0.099; 95% CI, 0.013-0.78; $p = 0.028$). For the secondary composite bleeding endpoint of major or CRNMB, 6% patients in each treatment arm had an event.

Caravaggio

The most recently published RCT investigating DOAC for the treatment of cancer-associated VTE is the Caravaggio study. This non-inferiority study compared apixaban with dalteparin in patients with active cancer or a diagnosis of cancer within the previous 2 years, and symptomatic or incidental proximal lower-limb DVT or PE.[25] The primary outcome was recurrent VTE. As in the ADAM VTE trial, patients received standard dose apixaban or dalteparin over 6 months. The Caravaggio study protocol was designed after the risk of major bleeding was observed to be increased with edoxaban and rivaroxaban versus dalteparin in patients with GI cancer.[44] To ensure patient safety, the Caravaggio study Data and Safety Monitoring Board received a mandate to monitor bleeding in patients with GI cancer,[44] who accounted for approximately 32% of the study population.[25]

Although the study protocol allowed for inclusion of patients with a history of cancer <2 years (up to 20% of the trial population),[44] the majority of patients had active cancer (>97%). Patients had a broad range of solid tumor types representative of a typical cancer population; tumors were metastatic in 68% of the study population; and, no anticancer therapy was excluded so patients were receiving a broad array of anticancer therapies, including antimetabolites (~20% of patients), platinum-based chemotherapy (~15%) and hormonal therapy (~10%), as well newer therapies, such as antiangiogenic monoclonal antibodies (~3%) and checkpoint inhibitors (~2%). In general, the baseline characteristics of the Caravaggio study population were comparable to those of the Hokusai VTE Cancer and SELECT-D studies.[23–25,45] The proportion of patients with upper GI cancer treated with a DOAC in the Caravaggio study (4%) was, however, slightly smaller than the proportion in the Hokusai VTE Cancer and SELECT-D trials (6% and 7%, respectively).[23–25] This may have reduced the risk of major GI bleeding with apixaban.

Recurrent VTE occurred in 5.6% of patients treated with apixaban and 7.9% of patients in the dalteparin group (HR 0.63; 95% CI, 0.37-1.07; $p < 0.001$ for non-inferiority; $p = 0.09$ for superiority), with no between-group difference in major bleeding (HR 0.82; 95% Cl 0.40-1.69). Event-free survival analysis showed a significant reduction in recurrent VTE, major bleeding or death with apixaban versus dalteparin (HR 0.74; 95% CI, 0.57-0.95). Although approximately one-third of the patients in Caravaggio had GI cancer, apixaban was not associated with an increased risk of major GI bleeding versus dalteparin (HR 1.05; 95% CI 0.44-2.50). Upper and lower GI bleeding occurred in similarly low proportions of patients treated with apixaban (0.9% and 1.0%, respectively) or dalteparin (1.0% and 0.7%, respectively). A subanalysis of the Caravaggio trial has shown that rates of major GI bleeding in patients with GI cancer were low and similar between the two treatment groups.[46] Lower GI bleeding occurred in 3 of 188 GI cancer patients in the apixaban treatment group and 3 of 187 patients in the dalteparin group, and upper GI bleeding occurred in 4 and 3 patients, respectively. There was a very slightly increased rate of major GU bleeding with apixaban (0.7% vs 0.2%), and GU bleeding contributed to a trend towards more CRNM bleeding (HR 1.42; 95% Cl 0.88-2.30) versus dalteparin.[25]

Meta-Analysis

A number of meta-analyses of RCTs of DOACs versus LMWH for the treatment of cancer-associated VTE have been performed.[42,47–52] A meta-analysis involving only the Hokusai

Table 3. Guideline recommendations for the treatment of cancer-associated VTE.[12,13,15,16,22,33]

Guideline	Recommendations	
	Initial treatment	Treatment duration
ACCP 2021	• Apixaban, edoxaban or rivaroxaban (strong recommendation). – Apixaban or LMWH may be preferred in luminal GI malignancies.	• Extended-phase (>3 months) DOAC therapy (apixaban, edoxaban or rivaroxaban) (strong recommendation) • Reassess periodically.
ASH 2021[a]	• DOAC (apixaban or rivaroxaban) or LMWH (conditional recommendation). – Caution with DOACs in GI cancers.	• Treat for 3–6 months with a DOAC (apixaban, edoxaban or rivaroxaban) over LMWH or VKA (conditional recommendations). • Treat for >6 months rather than short-term (3-6 months) in patients with active cancer (conditional recommendation). – Suggest continuing indefinitely rather than stopping after completion of a definitive period of anticoagulation (conditional recommendation). – Use a DOAC or LMWH (conditional recommendation).
NCCN 2021[a]	• Apixaban (category 1), edoxaban after ≥5 days of parenteral anticoagulation (category 1) or rivaroxaban (category 2A) preferred for patients without gastric or gastro-oesophageal lesions. – Caution in GU tract lesions. • LMWH preferred for patients with gastric or gastro-oesophageal lesions (category 1). • Dabigatran if above regimens not appropriate or unavailable.	• ≥3 months or as long as active cancer or cancer therapy.
ASCO 2019[b]	• LMWH, UFH, fondaparinux or rivaroxaban.	• Offer LMWH, DOACs or VKAs beyond the initial 6 months to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. – LMWH, edoxaban or rivaroxaban preferred. – LMWH preferred in settings with increased bleeding risk. • Assess intermittently to ensure a continued favorable risk-benefit profile.
ITAC 2019[b]	• LMWH when CrCl ≥30 mL/min (grade 1B). • Rivaroxaban (first 10 days) or edoxaban (started after ≥5 days' initial LMWH/UFHs) can be used for initial treatment if CrCl ≥30 mL/min and patient is not at high risk of GI or GU bleeding (grade 1B).	• LMWH or DOACs for ≥6 months (grade 1A) – DOACs when CrCl ≥30 mL/min if no impairment in GI absorption or strong DDIs (grade 1A), but caution advised in GI malignancies, especially upper GI tract. • After 6 months, termination or continuation of anticoagulation based on benefit-risk ratio, tolerability, drug availability, patient preference and cancer activity (guidance).
ISTH 2018[b]	• Patients with low bleeding risk and no DDIs: edoxaban or rivaroxaban; LMWHs are acceptable alternatives. • Patients with high bleeding risk[c]: LMWH; edoxaban or rivaroxaban as an alternative if no potential DDI.	• No specific recommendation

ACCP, American College of Chest Physicians; ASH, American Society of Hematology; ASCO, American Society of Clinical Oncology; CrCl, creatinine clearance; DDI, drug-drug interaction; ESC, European Society of Cardiology; GI, gastrointestinal; GU, genitourinary; ISTH, International Society on Thrombosis and Haemostasis; ITAC, International Initiative on Thrombosis and Cancer; LMWH, low molecular weight heparin; NCCN, National Comprehensive Cancer Network; DOAC, direct oral anticoagulant; PE, pulmonary embolism; RCT, randomized controlled trial; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a]Recommendations based on ADAM VTE, Caravaggio, Hokusai VTE Cancer and SELECT-D trial results;

[b]Recommendations based on Hokusai VTE Cancer and SELECT-D trial results;

[c]High bleeding risk includes patients with luminal gastrointestinal cancers with an intact primary; cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes; or active GI mucosal abnormalities (eg, duodenal ulcers, gastritis, esophagitis, or colitis).

VTE Cancer and SELECT-D studies showed the studied DOACs (edoxaban and rivaroxaban) to be more effective than dalteparin at preventing recurrent VTE, but both were associated with a significantly increased risk of major bleeding.[49] Meta-analyses aggregating results from the Hokusai VTE Cancer, SELECT-D and Carravaggio ± ADAM VTE trials employed different statistical methods but each reached similar conclusions, with the results favoring the studied DOACs (apixaban, edoxaban and rivaroxaban) in terms of efficacy, without a significant increase in major bleeding versus dalteparin (Table 2).[42,47,48,50–52] Contrasting with the non-significant increase in major bleeding observed in meta-analyses of all four RCTs, DOACs were associated with a significant increase in major bleeding when the Caravaggio trial was removed from analysis.[48]

A low level of heterogeneity and the consistency of efficacy results across Hokusai VTE Cancer, SELECT-D, ADAM VTE and Caravaggio reflect the generalizability of the improved efficacy of oral factor Xa inhibitors compared with dalteparin, and indicate that further studies are not likely to change this finding.[42,47,48] Although rates of major bleeding in DOAC-treated patients differed across the studies,[47] similarities were observed in the dalteparin control arms of the Hokusai Cancer VTE, SELECT-D and Caravaggio studies.[23–25] This raises the question as to whether differences in DOAC safety profiles are agent- or trial-specific.[42] Assessment of between-study heterogeneity showed that the apixaban trials (ADAM VTE and Caravaggio), in which overall major bleeding risk was not increased with apixaban versus dalteparin,[25,26] were the main contributors to major bleeding heterogeneity and may have influenced overall rates of major bleeding.[47] Potential explanations for differences in the risks of major bleeding between trials include heterogeneity in patient characteristics, protocol designs, distinct prespecified bleeding definitions, DOAC dose or frequency, or, other factors.[45] As shown in Table 1, the similar rates of major bleeding events in the dalteparin arms of the studies suggest that, overall, there weren't any large between-study differences in patient characteristics.[45] In the absence of any head-to-head comparisons of the different DOACs, it is, however, inappropriate to conclude that one DOAC is safer than another.[53]

Real-World Data

There is a lack of real-world evidence comparing the safety and efficacy of DOACs with LMWH for the treatment of cancer-associated VTE in Latin America, but encouraging outcomes have been reported for 35 patients with advanced cancer treated with rivaroxaban for VTE in Argentina who were followed for 1 year.[54] During this time, 3 patients had to stop DOAC therapy because of thrombocytopenia or jaundice related to the tumor and chemotherapy. There were 3 recurrent VTE events, 2 of which occurred after DOAC therapy was discontinued. All patients indicated that they were more compliant and comfortable with DOAC therapy than with LMWH injections.

Real-world data from a large retrospective analysis of US claims databases have also recently provided complementary evidence to Caravaggio regarding trends toward lower risks of recurrent VTE and major bleeding with apixaban versus LMWH.[55] In this real-world analysis, apixaban (n = 3393), LMWH (n = 6108) and the VKA warfarin (n = 4585) cohorts had active cancer (determined from medical claims for cancer diagnosis and treatment from 6 months before until 30 days after the index VTE event) and were very well matched for characteristics that influence the risk of VTE and bleeding, including age, metastases, type of malignancy and chemotherapy. In the overall population, apixaban was found to be associated with lower risks of recurrent VTE, major bleeding and CNRM relative to LMWH, and a lower risk of recurrent VTE versus warfarin. When follow-up was censored at 6 months, there was a 39% reduction in the risk of recurrent VTE in the apixaban cohort versus LMWH (HR 0.61; 95% CI, 0.47-0.81), and a 32% reduction versus warfarin (HR 0.68; 95% CI, 0.52–0.90). Compared with LMWH, patients receiving apixaban had a 37% reduction in the risk of major bleeding (HR 0.63; 95% CI, 0.47-0.86), as well as a lower risk of CNRM bleeding (HR 0.81; 95% CI, 0.70-0.94). Compared with warfarin, apixaban-treated patients had a similar risk of major bleeding (HR 0.73; 95% CI, 0.53-1.00) and CNRM bleeding (HR 0.89; 95% CI, 0.77-1.04). When using the entire follow-up period (maximum length of follow-up: approximately 3 years), results were generally consistent with 6 months' follow-up. Analyses of the data stratified by metastatic diagnosis, cancer-related treatment, chemotherapy, GI cancer and VTE event type (DVT only or PE with or without DVT) showed generally consistent results across the subgroups and with the overall population.[56] Apixaban had less major bleeding than LMWH regardless of metastases, cancer treatment, chemotherapy, GI cancer or VTE event type. In terms of recurrent VTE, there was some heterogeneity in relation to the presence of metastasis as risk was lower with apixaban versus LMWH in patients without metastases, whereas there was similar risk with apixaban and LMWH in patients with metastases. All point estimates favored apixaban in other high-risk subgroups.

Guidelines for the Treatment of Cancer-Associated VTE

In the absence of robust RCT evidence for DOACs versus LMWH for the treatment of cancer-associated VTE, practice guidelines published before 2018 uniformly recommended LMWH as the preferred treatment, and included no or relatively weak recommendations for DOACs as an alternative to LMWH.[57] Guidance for the treatment of VTE in primary care in Latin America published before 2018 states that although DOACs are a good option for the treatment of VTE in patients without cancer, they should be avoided in patients with cancer.[27] Adherence to these now outdated guidelines would mean that many patients would not receive anticoagulation in line with any of the RCT data using DOACs for the treatment of VTE in patients with active cancer.

More recently published guidelines from major societies, including updated guidelines from ACCP, ASH, ASCO and NCCN, generally recommend DOACs for patients without active GI or GU cancer who are not considered to be at high risk for bleeding on the basis of additional risk factors and are not taking concomitant medications that would lead to potentially serious drug–drug interactions with DOACs (Table 3).[12,13,15,16,22,33] Similarly, local expert recommendations from Argentina propose that DOACs will improve cancer patients' adherence to long-term anticoagulant therapy, and specify that DOACs are preferred for the treatment of VTE in low bleeding risk cancer patients without GI or GU tumors.[58] In addition to tumor type, risk factors for bleeding include thrombocytopenia, acute leukemia, severe renal impairment, severe hepatic impairment, intracranial metastatic disease, and active mucositis such as gastritis or esophagitis.[12,13,15,16]

The 2021 ACCP, NCCN and ASH guidelines, all of which were published post-Caravaggio, support use of apixaban, edoxaban or rivaroxaban in cancer patients with acute VTE.[16,22,33] ACCP guidelines strongly recommend treatment with apixaban, edoxaban or rivaroxaban over LMWH, but suggest that apixaban or LMWH may be the preferred option in patients with luminal GI malignancies.[22] NCCN guidelines specify that DOACs are preferred for patients without gastric or gastroesophageal lesions, with LMWH otherwise preferred.[16] ASH guidelines suggest LMWH or DOACs (rivaroxaban or apixaban) for initial treatment, and DOACs (apixaban, edoxaban or rivaroxaban) for short- to long-term anticoagulation, with caution advised in patients with GI cancer because of the higher risk of bleeding.[33] The most recent guidelines from ASCO, the International Society on Thrombosis and Haemostasis (ISTH) and the International Initiative on Thrombosis and Cancer (ITAC), none of which have been in a position to consider the Caravaggio or ADAM-VTE results, recommend DOACs, specifically edoxaban or rivaroxaban, for patients with non-GI cancers at low bleeding risk; otherwise LMWH remains the preferred anticoagulant.[12,13,15]

Recommendations for extended anticoagulation in cancer patients are mostly based on expert opinion as high quality data on extended treatment are generally limited to 6 months and do not go beyond the 12-month period.[59] Although the optimal duration of DOAC therapy is uncertain, there is consensus that anticoagulation should be continued for ≥3–6 months, or for as long as the cancer is active or under treatment, unless there are contraindications or unacceptable clinical risk.[12,13,15,16,22,33] In addition to the completed 12-month Hokusai-VTE Cancer study with edoxaban,[23] ongoing extended treatment studies include the 12-month EVE (NCT03080883) and API-CAT (NCT03692065) studies, which compare standard dose apixaban (5 mg twice daily) with stepped down 2.5 mg dosing.[26,59] Ideally, future studies would include a study of a DOAC versus placebo after 6 months of standard treatment if the cancer is no longer active or other thrombotic risk factors are resolved.

DOACs in Challenging Subgroups of Patients with Cancer-Associated VTE

Although recently published guidelines incorporate recommendations for the use of DOACs in the treatment of cancer-associated VTE, many management questions lack clinical trial data to inform recommendations and remain unaddressed.[32] GI tumors and pathology, extremes of body weight, thrombocytopenia, renal impairment and any other condition or drug (ie angiogenesis inhibitors) associated with increased risk of bleeding and/or recurrent VTE provide clinical challenges for which empiric management decisions must be made.[31,60,61] Further research is needed before DOACs can be recommended and used with confidence in these subgroups of patients. Towards this end, multiple Caravaggio subgroup analyses focusing on specific tumor types and comorbidities are ongoing.

GI Cancer

Whereas use of edoxaban and rivaroxaban is not recommended in patients with upper GI cancer because of an increased risk of major GI bleeding observed with these DOACS versus dalteparin in the Hokusai VTE Cancer and SELECT-D trials, the absence of an increased risk of major upper or lower GI bleeding with apixaban versus dalteparin in the Caravaggio trial suggests that apixaban could be a safe alternative to LMWH in patients with GI tumors. The incidence of major GI bleeding events in these trials was approximately 4% with edoxaban or rivaroxaban, 2% with apixaban and 1%–2% with dalteparin (Table 1).[23–25] Although it remains unclear whether apixaban is safer than edoxaban or rivaroxaban in patients with GI cancer, it is possible that compared with once-daily dosing, more stable plasma drug concentrations, with lower peaks and higher troughs, obtained with twice-daily dosing could have an impact on the safety profile of DOACs, as seen in patients with atrial fibrillation,[62,63] and contribute to reduced risk of GI bleeding with twice-daily apixaban versus once-daily edoxaban or rivaroxaban.[63] The mechanism of bleeding in GI cancer patients treated with DOACs also remains unclear, but in Hokusai VTE Cancer, upper GI bleeding was reported with edoxaban in all types of GI cancer regardless of location,[41] indicating that this DOAC may have a direct effect on the upper GI tract.

The Hokusai VTE Cancer and Caravaggio trials enrolled similar proportions of patients with GI cancer (~30% of patients), and approximately 5% of patients in both study populations had upper GI cancer.[23,25] Most of the major GI bleeding events reported with edoxaban in the Hokusai VTE Cancer trial occurred in patients with unresected upper GI tumors,[41] and all major GI bleeding events reported with apixaban in patients with GI cancer in the Caravaggio trial occurred in those with unresected tumors (5 of 121 patients with unresected colorectal cancer, 2 of 44 patients with unresected pancreatic or hepatobiliary cancer, 2 of 18 patients with unresected upper GI cancer).[46] Whereas 21% of patients receiving apixaban in Caravaggio had colorectal cancers, only 4% had upper GI

tumors so this group of patients might have been underrepresented. Therefore, although results with apixaban from the Caravaggio trial are promising, apixaban should be used with caution in patients with GI cancer, particularly those with upper GI tumors and/or intact primary GI tumors. There is also limited DOAC RCT data in patients after proximal GI surgery for tumor resection. Clinicians often rely on LMWH in such a setting to ensure adequate levels of anticoagulation when GI absorption may be compromised.[31,60]

GU Cancer

In general, treatment guidelines acknowledge a possible increase in the risk of GU tract bleeding with DOACs, and advise caution in patients with active GU tract lesions.[60] There was a suggestion of increased GU bleeding with apixaban and edoxaban in the Caravaggio and Hokusai VTE Cancer trials,[23,25] but numbers were small and it is difficult to reach a conclusion regarding GU bleeding risk. Meta-analyses of subgroup data aggregated from DOAC RCTs in cancer patients confirmed that GI and GU sites of major bleeding were more common with DOACs than with dalteparin,[42,47] and that DOACs were associated with a significantly greater risk of major bleeding than dalteparin in patients with GI cancer (risk ratio [RR] 2.55; 95% CI 1.24-5.27; $p = 0.01$), but not in patients with GU cancers (RR 2.81; 95% CI, 0.45-17.40; $p = 0.27$).[48]

Intracranial Tumors

Intracranial tumors are associated with an increased risk of VTE, but the risk of intracranial hemorrhage is also increased in these patients.[31] As a precautionary measure, patients with brain tumors or known intracerebral metastases were excluded from the Caravaggio trial.[25] Retrospective cohort study data published after the start of Caravaggio showed that DOACs did not increase the risk of intracranial hemorrhage compared with LMWH in patients with primary or metastatic brain tumors with brain lesions,[64] and patients who developed cerebral metastases during the Caravaggio trial were allowed to continue treatment. Furthermore, in the Hokusai VTE Cancer trial, which included 74 (7.1%) patients with primary or metastatic brain tumors (31 patients in the edoxaban treatment group and 43 in the dalteparin group), intracranial hemorrhage occurred in 0.4% of the edoxaban treatment group and 0.6% of the dalteparin group.[41] DOACs are therefore considered at least as safe in patients with primary or metastatic brain tumors but caution should be taken with some high bleeding risk intracranial tumors like metastatic melanoma.

Low Body Weight

Although helpful for informing treatment decision-making in Latin American populations, the RCT and real-world data for DOACs versus LMWH in the treatment of cancer-associated VTE are generally from North America and Europe. It may not be appropriate to simply extrapolate the results to other populations, which may vary in relation to bleeding and VTE risk factors other than tumor type. Clinicians in Latin America may, for example, have concerns about using full-dose DOACs in patients with low body weight (<60 kg), who were underrepresented in RCTs (~10% of patients) relative to the clinic, where at least 40% of patients have low body weight.[65] Whereas half-dose edoxaban was used in patients with body weight ≤60 kg in the Hokusai VTE Cancer trial,[23] there is no strong evidence for DOAC dose reduction in low-weight patients. Based on SELECT-D, ADAM VTE and Caravaggio,[23–25] in which all patients received full-dose rivaroxaban or apixaban, clinicians should feel comfortable using standard doses of these DOACs regardless of body weight.[60]

Renal Impairment

Patients with cancer may develop renal insufficiency as a result of malignancy, treatment or associated complications, with severe renal insufficiency increasing the risk of VTE and bleeding.[31,66] Most DOACs are at least partially renally cleared, and pivotal DOAC RCTs, both in general and cancer populations, excluded patients with creatinine clearance (CrCL) <30 mL/min (<25-30 mL/min for apixaban).[31] In general, DOACs should not be used in patients with CrCl <15 mL/min; edoxaban and rivaroxaban should be avoided or used with caution in patients with CrCl 15–29 mL/min; and, the daily edoxaban dose should be reduced from 60 mg to 30 mg in patients with CrCl 15–50 mL/min.[15,61,67,68] Apixaban exhibits minimal renal clearance, and full-dose apixaban can be used in patients with CrCl ≥15 mL/min, but questions remain as to whether full-dose apixaban is safe in patients with CrCl <30 mL/min.[31,67] In the Caravaggio trial, <10% of patients had CrCL ≤50 mL/min.[25] Dose-adjusted LMWH (with anti-Xa monitoring) is an appropriate alternative to apixaban in patients with CrCl <30 mL/min.[31,61]

Thrombocytopenia

Thrombocytopenia resulting from chemotherapy and/or malignancy is common in patients with cancer. In the setting of thrombocytopenia, the risk of bleeding is increased, but the risk of cancer-induced VTE remains.[31] Patients with acute leukemia were excluded from CARAVAGGIO because of the risk of increased bleeding associated with low platelet counts in these patients.[25] Furthermore, all four RCTs comparing DOACs versus LMWH in patients with cancer-associated VTE excluded patients with severe thrombocytopenia (Hokusai VTE Cancer and ADAM VTE trials: platelet count $<50 \times 10^9$/L; SELECT-D trial: $<100 \times 10^9$/L; Caravaggio: $<75 \times 10^9$/L),[23–26] so there are no data on the use of DOACs in this population. In the Caravaggio and Hokusai VTE Cancer trials, <5% of patients had a platelet count $<100 \times 10^9$/L.[23,25] Clinicians may therefore prefer to use dose-adjusted LMWH in patients with a platelet count $<50 \times 10^9$/L, but a half-dose DOAC has been suggested as a potentially acceptable alternative.[31] Care

should be taken when using DOACs in patients with an expected decrease in platelet count during chemotherapy.[61]

Incidentally Diagnosed VTE

In some regions of Latin America, the incidence of incidentally diagnosed VTE is increasing with the use of high-resolution CT-scanning for staging and follow-up of cancer patients. Incidental VTE was reported as the index event in approximately 20–50% of patients in the Hokusai VTE Cancer, SELECT-D and Caravaggio trials.[23–25] Based on data aggregated from the Hokusai Cancer VTE and Caravaggio trials with or without inclusion of SELECT-D, subgroup meta-analyses of patients with incidental VTE as the index event showed that the risks of recurrent VTE and major bleeding with DOACs versus dalteparin were consistent with outcomes in patients with symptomatic VTE as the index event, with the results favoring DOACs in terms of efficacy, without a significant increase in major bleeding.[42,50] Although clinicians may question whether all incidentally discovered VTE (eg visceral vein thrombi, subsegmental PE) should be treated with full-dose DOAC therapy,[53] the same therapeutic approach is advised for incidental and symptomatic cancer-associated VTE.[12,16,33]

Concomitant Cancer Treatment

Although DOACs have fewer DDIs than VKAs,[31] all DOACs are substrates of P-gp, and apixaban and rivaroxaban are also substrates of cytochrome P450 3A4 (CYP3A4).[69] Certain anticancer agents and some supportive care drugs can be inducers or inhibitors of CYP3A4 or P-gp, and may therefore increase or decrease the anticoagulant effect of DOACs.[30] Although patients treated with powerful inducers and/or inhibitors of CYP3A4 or P-gp were excluded from RCTs of DOACs for the treatment of CAT,[31,43] no anticancer therapy was included in the list of drugs excluded from Caravaggio.[70] Patients were therefore receiving a broad array of cytotoxic and biologic anticancer drug therapies, including medications associated with an increased risk of bleeding such as the antiangiogenic monoclonal antibodies bevacizumab, ramucirumab or aflibercept (~3% of patients).[25,70] Analysis of the effects of concomitant administration of anticancer agents, including antiangiogenic monoclonal antibodies and anticancer agents known to be inhibitors or inducers of P-gp and/or CYP3A4, did not appear to influence the incidence of VTE recurrence and major bleeding associated with apixaban in the Caravaggio study, suggesting that apixaban can be safely administered in patients with cancer-associated VTE receiving concomitant anticancer treatment.[70] Nevertheless, potential DDIs should be assessed before any DOAC is used in patients receiving chemotherapy or targeted cancer therapies.[31,43,61] Dose reduction to 2.5 mg twice daily is recommended for apixaban in patients receiving concurrent strong dual CYP3A4 and P-gp inhibitors, and to 30 mg daily for edoxaban in patients on concurrent potent P-gp inhibitors, while avoidance is recommended for other DOACs.[31]

The Place of DOACs in the Management of Cancer-Associated VTE in Latin America

Factor Xa inhibitor DOACs are a convenient, effective and safe option for many patients with cancer-associated VTE. DOACs represent a major step forward in the management of VTE in patients with active cancer in Latin America, and whenever possible use of these agents should be widely adopted in clinical practice. As patients with common cancers such as melanoma and lung cancer are living longer with active, metastatic disease, the risk of VTE is increasing, so more patients will experience VTE and require lifelong anticoagulation. These patients already carry a major burden of illness and long-term anticoagulation is generally much more achievable with a DOAC than with LMWH, although selection of DOAC versus LMWH therapy does need to be individualized according to bleeding risk, potential drug-drug interactions, cost, and patient preferences and needs, which should be assessed on a regular basis throughout their cancer VTE journey, when at times they may need parenteral therapies.

Primarily based on the Hokusai-VTE and SELECT-D trials results,[23,24] practice guidelines from major societies currently recommend factor Xa inhibitor DOACs for the treatment of VTE in patients with non-GI cancers at low bleeding risk with no potential for drug-drug interactions.[12,13,15,16,22] LMWH is preferred in all other patients. Recommendations for LMWH are particularly challenging in countries in Latin America, where LMWH is often prohibitively expensive, to the extent that patients may be admitted to hospital to receive unfractionated heparin via continuous infusion pump to avoid the high cost of outpatient LMWH injections for bridging therapy before starting VKA therapy.[27] Whereas there is no requirement for bridging therapy with apixaban or rivaroxaban, the need for an initial week of lead-in LMWH before the start of edoxaban treatment may limit the usefulness of this DOAC in Latin American countries.

In addition to Hokusai Cancer VTE and SELECT-D, the more recently reported Caravaggio and ADAM VTE trial results contribute to evidence of the consistent efficacy of factor Xa inhibitor DOACs in cancer-associated VTE, but have revealed some heterogeneity with respect to safety.[23–26] In terms of major bleeding and major GI bleeding, the Caravaggio and ADAM VTE study findings with apixaban compared favorably with those of the Hokusai-VTE cancer and SELECT-D trials of edoxaban and rivaroxaban, clearly showing no increased risk with apixaban versus dalteparin, as opposed to increased risk with edoxaban or rivaroxaban. In particular, the landmark Caravaggio trial has established the important role of DOACs for the treatment of cancer-associated VTE, showing that apixaban was non-inferior to dalteparin for the treatment of cancer-associated VTE without an increased risk of major lower or upper GI bleeding, despite approximately one-third of the population having GI cancer.[25] These findings may expand the proportion of cancer patients with VTE who are suitable for treatment with DOACs to include those with GI cancer, and will contribute to the evolution of international, regional and local treatment guidelines as they are updated.

In summary, published practice guidelines for the treatment of cancer-associated VTE in Latin America currently pre-date publication of the Caravaggio trial results, so although factor Xa inhibitor DOACs are preferred for patients with non-GI cancer, regional guidelines do not thus far recommend any of these DOACs for patients with GI cancer. The results of the Caravaggio trial should, however, help inform decision-making for the treatment of cancer-associated VTE going forward. In Latin American countries, LMWH is often not a viable treatment option, and clinicians should consider prescribing a factor Xa inhibitor DOAC as a practical, long-term alternative to LMWH for patients with active cancer. VKAs can be used in situations in which DOACs and LMWH are inaccessible and benefits outweigh the risks. The Caravaggio trial results support a recommendation for apixaban in patients with GI tumors, but caution is advised, particularly in patients with upper GI tumors or unresected lower GI tumors. The decision to use a DOAC in these patients requires careful consideration of bleeding risk, the cost-benefit and convenience of oral therapy, and patient preference. This is also the case when deciding whether to use a DOAC in other cancer populations at high bleeding risk, including patients with thrombocytopenia or severe renal impairment, for whom LMWH is often preferred. Inevitably, the use of DOACs for the treatment of VTE in patients with active cancer will vary in different countries of Latin America according to the level of access to the drugs and out-of-pocket purchase costs. Although DOACs are likely to be cheaper than LMWH, low-cost warfarin may be the only realistic treatment option in countries where drug cost is the ultimate decision driver.

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