International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer

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Abstract

Venous thromboembolism (VTE) is the second leading cause of death in patients with cancer. These patients are at an increased risk of developing VTE and are more likely to have a recurrence of VTE and bleeding while taking anticoagulants. Management of VTE in patients with cancer is a major therapeutic challenge and remains suboptimal worldwide. In 2013, the International Initiative on Thrombosis and Cancer (ITAC-CME), established to reduce the global burden of VTE in patients with cancer, published international guidelines for the treatment and prophylaxis of VTE and central venous catheter-associated thrombosis. The rapid global adoption of direct oral anticoagulants for management of VTE in patients with cancer is an emerging treatment trend that needs to be addressed based on the current level of evidence. In this Review, we provide an update of the ITAC-CME consensus recommendations based on a systematic review of the literature ranked according to the Grading of Recommendations Assessment, Development, and Evaluation scale. These guidelines aim to address in-hospital and outpatient cancer-associated VTE in specific [...]


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Venous thromboembolism (VTE) is the second leading cause of death in patients with cancer. These patients are at an increased risk of developing VTE and are more likely to have a recurrence of VTE and bleeding while taking anticoagulants. Management of VTE in patients with cancer is a major therapeutic challenge and remains suboptimal worldwide. In 2013, the International Initiative on Thrombosis and Cancer (ITAC-CME), established to reduce the global burden of VTE in patients with cancer, published international guidelines for the treatment and prophylaxis of VTE and central venous catheter-associated thrombosis. The rapid global adoption of direct oral anticoagulants for management of VTE in patients with cancer is an emerging treatment trend that needs to be addressed based on the current level of evidence. In this Review, we provide an update of the ITAC-CME consensus recommendations based on a systematic review of the literature ranked according to the Grading of Recommendations Assessment, Development, and Evaluation scale. These guidelines aim to address in-hospital and outpatient cancer-associated VTE in specific subgroups of patients with cancer.

Introduction
Cancer is an independent major risk factor for venous thromboembolism (VTE), which is the second leading cause of death in medically and surgically treated patients with cancer.1 The incidence of symptomatic and asymptomatic VTE is steadily increasing in these patients2-4 who are at an increased risk of VTE recurrence and bleeding, and are more likely to use health-care resources.5-7 As an independent prognostic factor for cancer progression and death,13 it has been recommended that VTE occurrence becomes a secondary endpoint in oncological trials.4

The clinical presentation of VTE—defined as deep vein thrombosis, pulmonary embolism, or central venous catheter-associated thrombosis—poses major therapeutic challenges that are further complicated by multiple cancer-related risk factors and comorbidities, which influence the choice of anticoagulation.8-12 Despite the development of national clinical practice guidelines (CPGs) on VTE treatment,11-18 substantial knowledge gaps remain.19 Preconceptions about patient tolerance and quality of life with the recommended anticoagulants need to be addressed as they hinder global CPG implementation. The International Initiative on Thrombosis and Cancer (ITAC-CME) initially published the 2013 international CPGs.19-21 Evidence-based knowledge was translated into clinical practice with a free web-based mobile application (for iOS and Android), in English and French, to improve patient care. In 2015, direct oral anticoagulants (DOACs) were prescribed in 20% of patients with cancer in the US22 and worldwide11 despite an absence of direct evidence to support this shifting clinical practice.23 As a result, the ITAC-CME developed an update of the 2013 recommendations to address DOAC use in the treatment of VTE for patients with cancer. In this Review, we summarise those results, and provide the first evidence-based international guidelines on DOAC use in the treatment of VTE. Guidelines were developed by an independent working group of academic experts, reviewed by an expanded global advisory committee, and endorsed by the International Society on Thrombosis and Haemostasis.

Guideline development
Critical appraisal
After suitable articles were selected from the literature search, critical appraisal (appendix p 9) of the selected articles’ methodological strength and clinical relevance was done independently by the methodologists (DF and JD) and then approved by the working group. Data were extracted into evidence tables and identified discrepancies were resolved by the working group. Conclusion tables that summarised the evidence for each clinical question were assembled to guide the development of the recommendations. The tables included rankings of the quality of evidence based on the types of studies (low, medium, high); the degree of agreement between studies (consistency); and an assessment of the patient population (directness) —ie, patients with cancer versus an unsselected study population, which was recorded as a study limitation.

The recommendations, developed during two consensus meetings, were formulated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) scale (panel 1).24,25,26 Additional economic considerations were taken into account during the development and ranking of the recommendations to offer treatment alternatives when possible that address potential economic barriers to treatment.

Review process
An independent medical education organisation—CME Solutions ULC (Montreal, QC, Canada), an organisation compliant with the Accreditation Council
for Continuing Medical Education for non-commercial interest in the USA and Canada—was appointed by the working group to impartially assemble the external global advisory committee. 56 experts from the global advisory committee were from relevant specialties and included national experts, international scientific societies and patient associations, three nurses, and two patient representatives (appendix p 78). They were identified on the basis of their knowledge, clinical expertise, publication record, and contributions to the field. Panel members were given an evaluation grid (nine point scale, from don’t agree to agree [0–9]) to complete. Feedback was analysed by the working group and revisions were incorporated into this Review.

**Guideline recommendations for the treatment of established VTE**

Recommendations on the treatment of established VTE for patients with cancer and the international advisory panel rankings of the guidelines can be found in panel 2.25,26

**Initial treatment (first 10 days)**

As presented in the 2013 CPGs,20 data pooled from randomised and retrospective studies indicated that patients with cancer who were initially treated with unfractionated heparin or low-molecular-weight heparin (LMWH) followed by a vitamin K antagonist (VKA) have a high prevalence of VTE recurrence (10·0–38·0% for unfractionated heparin and 6·7–17·0% for LMWH) and major bleeding (6·3–35·0% and 2·9–16·9%, respectively).

With regard to recommendations for short-term LMWH versus short-term unfractionated heparin followed by VKA, the 2013 CPGs were based on several meta-analyses25–28 of subgroups of patients with cancer comparing short-term LMWH, unfractionated heparin, or fondaparinux in the initial treatment of VTE in the general population.

Since our previous recommendations, two meta-analyses29,30 have compared short-term LMWH with unfractionated heparin in patients with cancer. One meta-analysis31 progressively expanded the subgroups of patients with cancer (1016 patients in 2008,35 801 in 2011,38 1606 in 201434), and consistently reported that VTE recurrence was not statistically different between patients receiving LMWH and those receiving unfractionated heparin. However, mortality in these studies was significantly reduced by 29·0% with LMWH at 3-month follow-up (3 months; 801 patients with cancer, relative risk [RR] 0·71, 95% CI 0·52–0·98) compared with unfractionated heparin, which was not observed in patients without cancer. In the second meta-analysis,36 LMWH significantly reduced overall mortality compared with unfractionated heparin by the end of treatment (3–6 months; 3816 patients with cancer; odds ratio [OR] 0·53, 95% CI 0·33–0·85).

Data on the use of inferior vena cava filters for VTE in patients with cancer are scarce. The 2013 CPGs with regard to use of IVCFs were based on 14 retrospective cohort studies (29–308 patients). Since the 2013 CPGs were published, one new randomised trial39 has compared recurrence of pulmonary embolism in patients assigned to inferior vena cava filters plus anticoagulation (33 [16·5%] of 200 patients had active cancer) versus anticoagulant alone (29 [14·6%] of 199 patients had active cancer). The recurrence for pulmonary embolism was doubled with inferior vena cava filters compared with anticoagulant alone at 3-month and 6-month follow-ups, although not statistically significantly (3·0% for inferior vena cava filter and anticoagulant at 3-month follow-up vs 1·5% anticoagulant alone at 3-month follow-up). Symptomatic deep vein thrombosis, major bleeding, 3-month and 6-month mortality, or inferior vena cava filter complications were not different between patients assigned to inferior vena cava filters plus anticoagulation and those assigned to anticoagulation alone. Another new randomised trial40 compared inferior vena cava filters plus fondaparinux with fondaparinux alone in 64 patients with different types of cancer; a third had either lymphoma, ovarian cancer, or an undefined histology. No differences between treatment groups were reported for inferior vena cava filter complications, major or minor bleeding, or survival at 90-day end-of-treatment follow-up. One new retrospective multicentre study41 examined in-hospital
all-cause mortality in 318,115 patients with cancer and pulmonary embolism at discharge from short-stay hospitals in the USA between 1998 and 2009. Overall, 69,635 (21·9%) of 318,115 patients with cancer and pulmonary embolism received an inferior vena cava filter. Mortality was lower for patients with inferior vena cava filters who were older than 30 years than in those without inferior vena cava filters (RR 0·68, 95% CI 0·67–0·70). Case fatality rates associated with an inferior vena cava filter varied according to tumour type. The in-hospital all-cause case fatality rates were higher with inferior vena cava filters than without in patients with haematological malignancies (RR 1·14, 1·07–1·21), except in elderly patients (>80 years), and in the case of lymphoma, patients aged 71–80 years also had lower case fatality rates.

**Early maintenance (10 days to 3 months) and long-term (beyond 3 months) treatment**

Seven randomised trials and eight meta-analyses have compared the benefit-to-risk ratio of LMWH versus unfractionated heparin. Although the two largest studies in this setting treated patients for 6 months, the strength of the evidence for treatment up to 6 months is low (inconsistency). Values and preferences: daily subcutaneous injection might be a burden for patients.

In the event of VTE recurrence, three options can be considered: (1) increase in LMWH dose (by 20–25%) in patients treated with LMWH; (2) switch from VKA to LMWH in patients treated with VKA; and (3) inferior vena cava filter insertion—with continued anticoagulant therapy, unless contraindicated (guidance, based on evidence of very low quality and an unknown balance between desirable and undesirable effects).

**Treatment of VTE recurrence in patients with cancer given anticoagulant treatment**

**Treatment of established catheter-related thrombosis**

**International Advisory Panel ranking: 8·79 out of 9·00**

1 For the treatment of symptomatic catheter-related thrombosis in patients with cancer, anticoagulant treatment is recommended for a minimum of 3 months; in this setting, LMWHs are suggested. Direct comparisons between LMWHs and VKAs have not been made in this setting (guidance).

2 The central venous catheter can be kept in place if it is functional, well positioned, and non-infected with good resolution of symptoms under close surveillance; irrespective of whether the central venous catheter is kept or removed, no standard approach in terms of duration of anticoagulation is established (guidance).
short-term heparin followed by VKA in the early maintenance and long-term treatment of confirmed VTE. Five clinical trials were done in patients with cancer (CLOT,25 CATCH,26 LITE,44 CANTHANOX,43 ONCENOX44) and two in unselected patients with VTE,25,46 some of whom had cancer (table 1). Four randomised trials25,26,42,46 assessed VTE recurrence. Three25,42,46 consistently reported a statistically significant 52·0–74·0% reduction in VTE with LMWH compared with heparin followed by VKA without increasing bleeds. In the CATCH study,26 long-term tinzaparin treatment was associated with a non-statistically significant reduction in a composite primary outcome measure of recurrent VTE (recurrent deep vein thrombosis, fatal or non-fatal pulmonary embolism, and incidental VTE), compared with short-term tinzaparin followed by VKA (7·2% with long-term tinzaparin vs 10·5% with short-term tinzaparin followed by VKA; hazard ratio [HR] 0·65, 95% CI 0·41–1·03; p=0·07). The proportion of patients with symptomatic deep vein thrombosis was significantly reduced in the long-term tinzaparin group (2·7% for long-term tinzaparin vs 5·3% for short-term tinzaparin followed by VKA; HR 0·48, 0·24–0·96; p=0·04), although this secondary outcome analysis was not adjusted for multiple comparisons. These results were not completely consistent with previous studies,25,42,44 possibly because the patient population from the CATCH trial26 had fewer thrombotic risk factors relative to other similar studies25,42,44 and was at lower risk of recurrent VTE, as indicated by the lower than expected recurrence of VTE in the tinzaparin followed by the VKA group.

The updated search identified one study47 that assessed extended LMWH treatment in patients with cancer and residual VTE after an initial 6 months of nadroparin (97 IU/kg twice a day). Patients with residual VTE were randomly assigned to either 6-month anticoagulation continuation (119 patients) or immediate anticoagulant discontinuation (123 patients). Patients without residual VTE discontinued anticoagulation (105 patients). No differences were observed in major bleeding between all three groups. Patients with residual VTE were at higher risk of VTE recurrence than were those with no residual VTE, irrespective of whether they received 6 months of extended LMWH prophylaxis or not. In a prospective multicentre cohort study,48 the proportion of patients with fatal recurrent pulmonary embolism and those patients with fatal bleeding were similar during the first 3 months of anticoagulation in the patients with cancer. After 3 months, case fatality rates associated with recurrent pulmonary embolism decreased, whereas fatal bleeds did not.

One prospective study published since 2013 compared VTE recurrence and major bleeding in 78 patients who received fondaparinux (six [7·7%] had 2·5 mg daily; 17 [21·8%] had 5 mg daily; 51 [65·4%] had 7·5 mg daily; four [5·1%] had 10 mg daily) with 3928 patients with LMWH (189 IU/kg [SD 65] daily) and found no differences in 3-month outcomes.49

DOACs have an easier route of administration (oral) compared with anticoagulants that are administered by parenteral injection, and have fixed-dose regimens with predictable anticoagulant effects,50 but their absorption might be affected by vomiting, which occurs in up to 50·0% of patients with cancer.51 Drug interactions between DOACs and chemotherapy agents and antiangiogenic therapies are a risk. P-glycoprotein transport and CYP3A4 metabolic pathways are inhibited by tyrosine-kinase inhibitors and hormonal therapies, and are induced by doxorubicin, vinblastine, and dexamethasone,52 which might result in reduced responses to chemotherapy and an increased risk of bleeding by altering the serum concentration of DOACs. LMWH is not associated with risk of interaction with chemotherapy, nor does it rely on oral intake or gastrointestinal absorption.48 However, it does have a more onerous route of administration, since it requires weight adjustment of the dose, and can be associated with heparin-induced thrombocytopenia. Before 2015, there were no antidotes to immediately reverse the actions of the DOACs in case of bleeding.52 However, idarucizumab has become available as an antidote to dabigatran.53 Two other antidotes are under different stages of development: andexanet alfa is undergoing phase 3 trials as an antidote for the factor Xa inhibitors

<table>
<thead>
<tr>
<th>Patients with cancer</th>
<th>Number of patients</th>
<th>LMWH</th>
<th>Dosage and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOT; Lee et al (2003)45</td>
<td>672</td>
<td>Dalteparin</td>
<td>200 IU/kg once per day for 1 month, 150 IU/kg per day for 5 months</td>
</tr>
<tr>
<td>CATCH; Lee et al (2015)46</td>
<td>900</td>
<td>Tinzaparin</td>
<td>175 IU/kg once per day for 6 months</td>
</tr>
<tr>
<td>LITE; Hull et al (2006)46</td>
<td>200</td>
<td>Tinzaparin</td>
<td>175 IU/kg once per day for 3 months</td>
</tr>
<tr>
<td>CANTHANOX; Meyer et al (2002)43</td>
<td>146</td>
<td>Enoxaparin</td>
<td>1·5 mg/kg once per day for 3 months</td>
</tr>
<tr>
<td>ONCENOX; Deitcher et al (2005)44</td>
<td>122</td>
<td>Enoxaparin</td>
<td>1 mg/kg twice per day for 5 days, 1·0 mg/kg or 1·5 mg/kg once per day for 6 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unselected patients</th>
<th>Number of patients</th>
<th>LMWH</th>
<th>Dosage and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez-Beret et al (2001)48</td>
<td>158</td>
<td>Nadroparin</td>
<td>0·1 ml/10 kg twice per day for 3 to 6 months</td>
</tr>
<tr>
<td>Romera et al (2009)49</td>
<td>241</td>
<td>Tinzaparin</td>
<td>175 IU/kg once per day for 6 months</td>
</tr>
</tbody>
</table>

Early maintenance was 10 days to 3 months. Long-term treatment was more than 3 months. LMWH=low-molecular-weight heparin.

Table 1: Trials comparing LMWH with LMWH plus vitamin K antagonists in early maintenance and long-term treatment of venous thromboembolism.
Betrixaban, is undergoing phase 3 trials.\textsuperscript{56,57} The DOACs and three factor Xa inhibitors: rivaroxaban, apixaban, and edoxaban include a thrombin inhibitor (dabigatran),\textsuperscript{48} 4832 patients in EINSTEIN-PE 65) compared rivaroxaban vs\textsuperscript{70} RE-COVER II [1280 patients treated with dabigatran vs 1266 patients treated with VKA]; 67\textsuperscript{70} RE-COVER II [1280 patients treated with dabigatran vs 1288 patients treated with VKA]). Patients with a glomerular filtration rate of less than 30 mL/min were excluded. A prespecified pooled analysis of the two trials examined safety and efficacy outcomes in 597 patients with active cancer (430 at inclusion, 167 diagnosed during the study).\textsuperscript{70} At the end of treatment (approximately 200 days), rivaroxaban was non-inferior to short-term LMWH followed by VKA with regard to VTE recurrence (5·1% with rivaroxaban vs 7·1% with short-term LMWH followed by VKA; HR 0·69, 95% CI 0·36–1·33), major bleeding (2·8% vs 5·0%; HR 0·23–1·23), and in a composite of clinically relevant non-major and major bleeding (15·2% vs 17·0%; HR 0·62–1·41).

Two randomised phase 3 clinical trials compared dabigatran with VKA in acute VTE treatment for more than 6 months (RE-COVER [1127 patients treated with dabigatran vs 1266 patients treated with VKA];\textsuperscript{70} RE-COVER II [1280 patients treated with dabigatran vs 1288 patients treated with VKA]). Patients with a glomerular filtration rate of less than 30 mL/min were excluded. Participants initially received LMWH or
unfractionated heparin for at least 5 days, followed by 6 months of dabigatran at 150 mg twice a day or a VKA. 335 (6-6%) of 5107 study participants across both RECOVER trials combined had an active cancer (221 at baseline, 114 diagnosed during the study). The dabigatran treatment group had a recurrence of VTE that was similar to VKA for both cancer at baseline (HR 0·75, 95% CI 0·20–2·8) and cancer diagnosed during the study (HR 0·63, 0·20–2·0), with no differences in major and clinically relevant non-major bleeding (cancer at baseline: HR 1·48, 0·64–3·4; cancer diagnosis during study: HR 0·65, 0·27–1·6). These data are from a pooled analysis of both RECOVER trials.69

The AMPLIFY trial70 (5400 patients) compared apixaban (10 mg twice a day for 7 days, then 5 mg twice a day) with LMWH followed by a VKA for acute VTE treatment for 6 months. Patients with a glomerular filtration rate of less than 25 mL/min were excluded. In 534 patients with cancer (169 with active cancer; 365 with a history of cancer), VTE recurrence (RR 0·56, 95% CI 0·13–2·37) and major bleeding (RR 0·45, 0·08–2·46) were similar in both treatment groups. In patients with a history of cancer only, VTE recurrence was significantly reduced with apixaban compared with LMWH plus VKA (1·1% vs 6·3%; RR 0·17, 0·04–0·78), with no significant differences in major bleeding (0·5% vs 2·8%; RR 0·20, 0·02–1·65).71

The HOKUSAI-VTE phase 3 trial72 randomised 8292 participants to edoxaban or a VKA for 3–12 months. Patients with a 30–50 mL/min glomerular filtration rate received a 50% dose of edoxaban, and those with a glomerular filtration rate of less than 30 mL/min were excluded. A post-hoc analysis assessed the safety and efficacy of edoxaban in 771 patients with active cancer or a history of cancer (9·3% of the study population).72,73 In 208 patients with active cancer, VTE recurrence was similar between treatment groups (HR 0·55, 95% CI 0·16–1·85), with no significant differences in major and clinically relevant non-major bleeding (HR 0·37, 0·02–1·65). These data are from a pooled analysis of both RECOVER trials.69

Seven meta-analyses74–80 have examined the role of DOACs in the treatment and secondary prevention of acute VTE since 2013. When including six randomised DOAC trials with a documented cancer subgroup,75,77,78,79 VTE recurrence was 3·9% (23 of 595 patients) with DOAC versus 6·0% (32 of 537 patients) with VKA in 1132 patients with cancer.77 The proportion of patients who had VTE while on DOAC treatment was reduced by approximately 35·0% compared with that in the VKA group, although not significantly (OR 0·63, 95% CI 0·37–1·10). The proportion of patients with major bleeding (3·2% in the DOAC group vs 4·2% in the heparin followed by VKA group; OR 0·77, 95% CI 0·41–1·44) and minor bleeding (14·5% vs 16·5%; OR 0·85, 0·62–1·18) were similar between the two treatment groups. Another meta-analysis75 of these trials reported consistent findings. When analysing the same six clinical trials, but with a broader inclusion of 1581 patients with cancer, the composite efficacy endpoint combining recurrent VTE and VTE-related death was significantly reduced with a DOAC (27 [3·4%] of 805 patients with a DOAC vs 46 [5·9%] of 776 patients with a VKA; RR 0·57, 0·36–0·91) with no differences in major bleeding between treatments (RR 0·77, 0·44–1·33). Meta-analyses that were limited to fewer phase 3 trials reported similar findings.77,78

In the absence of studies that compared DOACs with LMWH in patients with cancer, one pairwise meta-analysis included nine prospective studies of patients with cancer with acute symptomatic deep vein thrombosis or pulmonary embolism, or both, randomly assigned to receive LMWH alone, a DOAC, or a VKA. Although LMWH was associated with reduced VTE recurrence versus VKA (RR 0·52, 95% CI 0·36–0·74), DOACs had a similar VTE recurrence to VKA (RR 0·66, 0·39–1·11). No significant differences in major bleeding were observed; compared with VKA, LMWH was associated with a non-significant increase in major bleeding and DOACs were associated with a non-significant reduction (LMWH: RR 1·06, 0·5–2·23; DOAC: RR 0·78, 0·42–1·44). An indirect network meta-analysis80 estimated the relative efficacy and safety of DOACs compared with LMWH. Preliminary pairwise comparisons indicated that the risk of VTE recurrence was significantly reduced with LMWH compared with VKA (RR 0·60, 95% CI 0·45–0·79; p=0·001), without increasing risk of major bleeding (RR 1·07, 0·66–1·73; p=0·80). DOACs versus VKA had comparable recurrence of VTE (RR 0·65, 0·38–1·09; p=0·10) and major bleeding (RR 0·72, 0·39–1·35; p=0·31). The indirect network meta-analysis, which used VKA as the common comparator, showed that the risk of recurrent VTE (RR 1·08, 0·59–1·95; p=0·81) and major bleeding (RR 0·67, 0·31–1·46; p=0·31) might be similar between LMWH and DOAC.

VTE recurrence in patients with cancer on anticoagulation medication

Studies assessing therapeutic strategies for VTE recurrence are scarce. The 2013 international CPGs relied on one retrospective cohort study81 in 70 patients with cancer and recurrent VTE undergoing anticoagulation treatment. Several retrospective or prospective cohort studies have analysed the use of inferior vena cava filters in the prevention of VTE recurrence,82 including one systematic review80 of 6834 patients (number with cancer unspecified) that was not identified in the 2013 guidelines, with inconsistent findings.
Treatment of established central venous catheter-associated thrombosis

Symptomatic catheter-associated thrombosis occurs in 3·0–5·0% of patients with cancer requiring venous access, which increases to as much as 30·0% when including asymptomatic cases.21

Since 2013, one new retrospective study49 assessed LMWH for symptomatic catheter-associated thrombosis in 99 patients with cancer. 72 (72·7%) patients received full-dose LMWH for 1 month followed by an intermediate dose for 3, 6, or 12 months, with no recurrence. In the 13 patients receiving a preventive dose of LMWH after 3, 6, or 12 months at full or intermediate doses, two (15·4%) had VTE recurrence. A second retrospective study50 in 35 patients with acute leukaemia reported that 17 (81·0%) of 21 patients had VTE resolution with high-dose or low-dose enoxaparin, compared with six (42·9%) of 14 patients not on anticoagulants (p=0·11). The prevalence of mortality was 33·3% for patients treated with enoxaparin versus 71·4% for patients who did not receive anticoagulation (HR 0·32, 95% CI 0·12–0·85).

One meta-analysis51 assessed the benefit-to-risk ratio of different anticoagulants in 2564 patients with catheter-associated thrombosis. LMWH or unfractionated heparin at prophylactic doses significantly reduced symptomatic deep vein thrombosis by 50% compared with no heparin, with no differences in major or minor bleeding, mortality, or thrombocytopenia. A similar safety and efficacy profile to LMWH and unfractionated heparin was found for VKA, but quality of this evidence was ranked as low.

The reported prevalence of incidental VTE varies between 2·0% and 7·3% depending on VTE site and cancer type.86,87 Some studies suggest that as many as 3·0–5·0% of patients with cancer requiring venous access, which increases to as much as 30·0% when including asymptomatic cases.21

Our review included data from 14 new prospective studies on the efficacy and safety of prophylactic LMWH, unfractionated heparin, or fondaparinux in patients with cancer undergoing surgery. Nine new prospective studies assessed the efficacy and safety of prophylactic LMWH in patients with cancer undergoing surgery. Two randomised clinical trials assessed extended-duration prophylaxis in patients with cancer after major abdominal or pelvic surgery, and reported a decrease in VTE without increasing major or minor bleeding (626 patients;96 225 patients 97). The latest randomised study52 compared LMWH prophylaxis (group A) with extended-duration prophylaxis (group B, an additional 3 weeks) after laparoscopic cancer surgery. Extended-duration prophylaxis reduced VTE occurrence at the end of treatment (28 days [SD 2]); 9·7% in group A vs 0·0% in group B; p=0·001) and at 3 months after surgery, with no differences in bleeding.

One new prospective study53 assessed perioperative inferior vena cava filter use for primary cytoreductive surgery in 274 patients with ovarian, fallopian tube, or primary peritoneal cancer receiving LMWH. Of the 38 patients with an inferior vena cava filter, 20 underwent filter placement for VTE. Five (25·0%) of these 20 patients had VTE recurrence with an inferior vena cava filter (effective period of filter placement between 4 weeks before and 6 weeks after the primary cytoreductive surgery), compared with a VTE recurrence of one (5·9%) of 17 patients receiving inferior vena cava filters for a non-VTE indication. 17 (7·2%) of 237 patients without an inferior vena cava filter developed VTE. The cumulative risk of metastasis or disease progression was 45·2% with an inferior vena cava filter versus 13·6% for those without an inferior vena cava filter (HR 4·35, 95% CI 2·04–9·25; p<0·001). Median survival was 5·7 months with an inferior vena cava filter versus 15·3 months without (p=0·001).

Since the 2013 CPGs, one randomised study54 assessed the safety and efficacy of external compression devices in 220 patients with cancer undergoing gastric surgery. External compression devices plus LMWH was associated with reduced VTE incidence and significant increased risk of bleeding compared with the use of an external compression device alone.

Guideline recommendations for VTE prophylaxis in patients with cancer

Recommends for VTE prophylaxis in patients with cancer and the corresponding international advisory panel rankings can be found in panel 3. VTE risk-assessment models are provided to guide anticoagulant-treatment decisions (panel 4).98–90

Patients with cancer undergoing surgery

A systematic review55 of 14 randomised trials that was not in the 2013 CPGs has been identified. The review compares VTE prophylaxis with placebo or no intervention in women undergoing benign or oncological gynaecological surgery. VTE prevalence ranged 0·0–34·6% in patients with cancer without prophylaxis, compared with 0·0–14·8% in oncology patients receiving prophylaxis.

One meta-analysis56 compared LMWH with unfractionated heparin in perioperative VTE prophylaxis across 16 randomised controlled trials (12 890 patients with cancer). Consistent with an earlier version of this meta-analysis57 and a meta-analysis in general surgery,56 perioperative prophylaxis with LMWH once a day produced effects on symptomatic and asymptomatic deep vein thrombosis that were similar to those with unfractionated heparin three times a day (RR 0·78, 95% CI 0·53–1·15), and superior to unfractionated heparin twice a day (RR 0·66, 0·44–0·99). The search did not identify any new studies that compared different anticoagulants or different doses of LMWH in patients with cancer undergoing surgery.

Two randomised clinical trials assessed extended-duration prophylaxis in patients with cancer after major abdominal or pelvic surgery, and reported a decrease in VTE without increasing major or minor bleeding (626 patients;96 225 patients 97). The latest randomised study52 compared LMWH prophylaxis (group A) with extended-duration prophylaxis (group B, an additional 3 weeks) after laparoscopic cancer surgery. Extended-duration prophylaxis reduced VTE occurrence at the end of treatment (28 days [SD 2]); 9·7% in group A vs 0·0% in group B; p=0·001) and at 3 months after surgery, with no differences in bleeding.

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Review

Medically treated patients with cancer
The 2013 CPGs were based on findings from the general medically ill patient population admitted to hospital, 5.0–15.0% of whom had cancer. The updated search identified one randomised trial (CERTIFY) of 274 patients with cancer that found similar VTE prevalence between patients who received 3000 IU certoparin once a day and those who received 5000 IU unfractionated heparin three times a day (4.5% with certoparin vs 6.0% with unfractionated heparin; OR 0.73, 95% CI 0.23–2.39). The occurrence of major bleeds was similar between groups, with a non-significant increase in minor bleeding in the unfractionated heparin group. Since 2013, one meta-analysis assessed LMWH prophylaxis in 307 patients with cancer from three placebo-controlled randomised trials (including 5134 hospital-admitted medical patients). By contrast with the general medically ill, hospital-admitted population, 40 mg enoxaparin, 5000 IU dalteparin, or 2.5 mg fondaparinux once a day did not significantly

Panel 3: Prophylaxis in venous thromboembolism in patients with cancer

Prophylaxis of venous thromboembolism (VTE) in surgically treated patients with cancer
International Advisory Panel ranking: 8.60 out of 9.00
1 Use of low-molecular-weight heparin (LMWH) once per day or low-dose unfractionated heparin (UFH) three times per day is recommended to prevent postoperative VTE in patients with cancer; pharmacological prophylaxis should be started 12–2 h preoperatively and continued for at least 7–10 days; no data are available to allow conclusions regarding the superiority of one type of LMWH over another (grade 1A).
Values and preferences: LMWH once per day is more convenient.
2 Evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer is insufficient (grade 2C).
Values and preferences: similar.
3 Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in patients with cancer is recommended (grade 1A).
Values and preferences: equal (no preferences).
4 Extended prophylaxis (4 weeks) with LMWH to prevent postoperative VTE after major laparotomy in patients with cancer is indicated in patients with a high VTE risk and low bleeding risk (grade 1B).
Values and preferences: longer duration of injections.
5 Extended prophylaxis (4 weeks) with LMWH for the prevention of VTE in patients with cancer undergoing laparoscopic surgery is recommended in the same way as for laparotomy (grade 2C).
Values and preferences: daily injections.
Costs: in some countries, the price of LMWH might influence the choice.
6 Mechanical methods are not recommended as monotherapy, except when pharmacological methods are contraindicated (grade 2B).
Values and preferences: no injection.
7 Inferior vena cava filters are not recommended for routine prophylaxis (grade 1A).

Prophylaxis of VTE in medically treated patients with cancer
International Advisory Panel ranking: 8.54 out of 9.00
1 We recommend prophylaxis with LMWH, UFH, or fondaparinux in medically treated patients with cancer and reduced mobility who are admitted to hospital (grade 1B). In this setting, direct oral anticoagulants are not recommended routinely (guidance).
Values and preferences: subcutaneous injections.
Costs: in some countries price differences between LMWH, UFH, or fondaparinux might influence the choice.
2 Primary prophylaxis with LMWH, vitamin K antagonists, or direct oral anticoagulants in patients receiving systemic anticancer therapy is not recommended routinely (grade 1B).
Values and preferences: subcutaneous injections.
3 Primary pharmacological prophylaxis of VTE with LMWH is indicated in patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low bleeding risk (grade 1B).
Values and preferences: subcutaneous injections.
4 Primary pharmacological prophylaxis of VTE might be indicated in patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy and who have a low bleeding risk (grade 2C).
Values and preferences: subcutaneous injections.
5 In patients treated with thalidomide and lenalidomide combined with steroids or other systemic anticancer therapies, or both, VTE primary pharmacological prophylaxis is recommended (grade 1A); in this setting, vitamin K antagonists at low or therapeutic doses, LMWH at prophylactic doses, and low-dose aspirin can be used and have shown similar effects with regard to preventing VTE (grade 2C).
Values and preferences: subcutaneous injections.

Prophylaxis of catheter-related thrombosis
International Advisory Panel ranking: 8.45 out of 9.00
1 Use of anticoagulation for routine prophylaxis of CRT is not recommended (grade 1A).
Values and preferences: bleeding risk with anticoagulants.
2 Catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium (grade 1B).
reduce the VTE relative risk compared with placebo in hospital-admitted patients with cancer (RR 0·91, 95% CI 0·21–4·0; P=68%).

The MAGELLAN trial assessed rivaroxaban for VTE prophylaxis in 8101 hospital-admitted, medically ill patients, including 592 (7·3%) patients with active cancer. Rivaroxaban (10 mg once a day) was compared with enoxaparin (40 mg) for the first 10 days. Patients receiving rivaroxaban were maintained on the same regimen for an additional 35 days, whereas the enoxaparin group received a placebo after day 10. In patients with active cancer, VTE prevalence was similar between rivaroxaban and enoxaparin (9·9% for rivaroxaban vs 7·4% for enoxaparin). Similar to the results reported in the whole study population, rivaroxaban increased the risk of clinically relevant bleeding in patients with active cancer compared with enoxaparin (5·4% for rivaroxaban vs 1·7% for enoxaparin).

**Ambulatory patients treated with systemic anticancer therapy**

The updated search identified eight meta-analyses (1669–9861 patients) and six randomised clinical trials comparing anticoagulant prophylaxis with no intervention or placebo in ambulatory patients receiving systemic anticancer therapy. Overall, a significant 45·0% reduction in VTE occurrence was reported across the six meta-analyses assessing the safety and efficacy of LMWH compared with no intervention or placebo. Specific cancer subgroup analyses across the meta-analyses showed that LMWH significantly reduced the VTE prevalence compared with no treatment or placebo by 67·9–71·2% in patients with pancreatic cancer (range of 430–748 patients) and by 50·3–53·6% in patients with lung cancer (range of 1926–2075 patients). Five of six meta-analyses reported no significant increase in major bleeding with LMWH (13·0–30·0% of patients received LMWH and had major bleeding) compared with no prophylaxis. The sixth study reported that patients were 65·0% more likely to experience a bleeding event with LMWH (7875 patients in the total population across the 11 studies; OR 1·65, 95% CI 1·12–2·44) compared with no intervention. All studies reported a significant increase in minor bleeding in the LMWH prophylaxis group. No significant difference in 1-year mortality was reported by any of the meta-analyses.

The effects of VTE prophylaxis in pancreatic and lung cancer subgroup meta-analyses suggest a more robust anticoagulant benefit-to-risk ratio in these populations. The FRAGEM randomised controlled trial compared gemcitabine plus weight-adjusted dalteparin (200 IU/kg once a day for 4 weeks, then 150 IU/kg for a further 8 weeks) with gemcitabine alone in 123 patients with advanced pancreatic cancer. Prevalence of VTE was 23·0% in the control group versus 3·4% with anticoagulation treatment after treatment for less than 100 days (RR 0·145,
Three randomised clinical trials (TOPIC-1 [353 patients], TOPIC-2 [547 patients], and FRAGMATIC [2202 patients]) and one meta-analysis assessed VTE prophylaxis in patients with lung cancer. The TOPIC study included two double-blind trials comparing the LMWH certoparin (3000 IU per day) with placebo in ambulatory patients with metastatic breast cancer (TOPIC-1) or with stage III or IV non-small-cell lung carcinoma (NSCLC; TOPIC-2). VTE occurrence did not differ between treatment groups for TOPIC-1 or TOPIC-2. However, a separate post-hoc analysis showed that certoparin significantly reduced VTE occurrence in patients with stage IV NSCLC compared with placebo (3.5% with certoparin vs 10.2% with placebo, p=0.032; appendix p 39) without increasing bleeds. Mortality was not different between groups. The FRAGMATIC multicentre, open-label, randomised trial assessed LMWH prophylaxis on 1-year survival in newly diagnosed patients with small-cell lung cancer or those with NSCLC of any stage. LMWH did not increase overall survival or metastasis-free survival. However, VTE risk was lower with LMWH than without primary prophylaxis (5.5% vs 9.7%; HR 0.57, 95% CI 0.42–0.79). Major bleeding did not differ between groups, but a composite measure of major plus clinically relevant non-major bleeding was higher with the addition of LMWH. In the meta-analysis (2185 patients), 1-year and 2-year survival benefits of anticoagulation (VKA or heparin) were reported in limited-stage, but not advanced-stage, patients with cancer. Anticoagulation significantly improved overall 1-year (RR 1.18, 95% CI 1.06–1.32, p=0.004) and 2-year (RR 1.27, 1.04–1.56, p=0.02) survival in patients with lung cancer. However, subgroup analyses indicated that survival benefits were statistically significant in limited-stage patients with cancer (RR 1.30, 1.03–1.65, p=0.03 for 1-year survival; RR 1.33, 1.05–1.68, p=0.02 for 2-year survival) but not advanced-stage patients with cancer (RR 1.09, 0.87–1.36, p=0.48 for 1-year survival; RR 1.16, 0.77–1.73 for 2-year survival), and in small-cell lung cancer (RR 1.21, 1.07–1.38, p=0.003 for 1-year survival; RR 1.29, 1.01–1.65, p=0.04 for 2-year survival) but not in patients with NSCLC (RR 1.10, 0.87–1.39 for 1-year survival; RR 1.24, 0.86–1.78 for 2-year survival). Compared with control, anticoagulation significantly reduced the VTE risk (RR 0.55, 0.31–0.97).

Since the 2013 CPGs, one new meta-analysis of 1669 patients assessed the effects of VKAs versus placebo or no intervention in primary VTE prophylaxis. A non-significant decrease in VTE in patients on VKA was reported (RR 0.15, 95% CI 0.02–1.2; p=0.074), with a significant sizeable increase in major bleeding (RR 4.24, 1.86–9.65) and minor bleeding (RR 3.19, 1.83–5.55).

A phase 2 dose-finding, double-blind, randomised study (ADVOCATE) assessed the safety and tolerability of apixaban prophylaxis in 125 ambulatory patients with advanced or metastatic cancer receiving chemotherapy. Apixaban prophylaxis was started within 4 weeks of initiating chemotherapy and lasted for 12 weeks. The proportion of patients with VTE was three (10.3%) of 29 patients in the placebo group, and no (0%) patients in the apixaban group (32 in the 5 mg group, 29 in the 10 mg group, and 32 in the 20 mg group). No major bleeding incidents were reported with either a 5 mg or 10 mg dose of apixaban, but two (6.3%) of 32 patients had a major bleed in the 20 mg group.

One retrospective analysis of the PROTECHT trial, which was not identified in the 2013 CPGs, assessed the benefit to risk of LMWH thromboprophylaxis in 1150 patients with initiation of chemotherapy for a maximum of 120 days. Nadroparin (3800 anti-Xa IU once a day) reduced VTE risk by 68.0% in patients receiving gemcitabine alone and by 78.0% when combined with a platinum-based agent.

Two randomised studies (with 342 patients and 991 patients) and one meta-analysis of 6632 patients that were not identified in the 2013 CPGs compared LMWH thromboprophylaxis with aspirin or warfarin in patients treated with thalidomide or lenalidomide with multiple myeloma. Overall, these studies indicated that prophylactic doses of LMWH, aspirin (100 mg per day), or warfarin reduced the risk of VTE in patients with myeloma treated with lenalidomide or thalidomide without increasing bleeding complications. None of the studies included a placebo group.

**Prophylaxis of central venous catheter-associated thrombosis**

One new meta-analysis, which pooled the effect of different anticoagulants, reported a reduction in symptomatic catheter-associated thrombosis in patients with cancer and a central venous catheter (RR 0.61, 95% CI 0.42–0.88; 3018 patients in total). Another new meta-analysis assessed VTE prophylaxis in paediatric patients with cancer with tunnelled central venous catheters. Treatment with LMWH (n=134); low-dose warfarin (n=31); antithrombin (n=37); cryoprecipitate or fresh frozen plasma, or both (n=240); or antithrombin plus LMWH (n=41) produced a similar proportion of VTE occurrences to no intervention. However, concomitant LMWH and antithrombin supplementation reduced symptomatic VTE without an increase in bleeding. Since 2013, one new meta-analysis reported that peripherally
inserted central venous catheters are associated with a higher risk of deep vein thrombosis compared with other central venous catheters, particularly in critically ill patients or patients with cancer.

**VTE treatment in special clinical situations**

Recommendations on VTE treatment for patients in special clinical situations can be found in panel 5.

**Patients with brain tumours**

One new retrospective study[^24] assessed the risk of intracranial haemorrhage associated with VTE anticoagulation in 293 patients with cancer with brain metastases. Therapeutic doses of enoxaparin did not increase intracranial haemorrhage, including in patients with melanoma and renal-cell carcinoma, who in control cohorts had a four times increased risk of intracranial haemorrhage relative to other types of cancer.

One randomised, placebo-controlled, double-blind clinical trial (186 patients with brain tumours) assessed VTE prophylaxis with dalteparin treatment (5000 IU once a day). LMWH was not associated with a significant reduction in VTE occurrence or in mortality.[^25] Major bleeding was not significantly increased, but the CI was large (HR 4.2, 95% CI 0.48–36), and all major bleeds were intracranial. Since 2013, one meta-analysis[^26] (2208 patients) reported that the proportion of patients with VTE was 4.3% with bevacizumab alone, 4.2% when added to chemotherapy, and 4.2% with the addition of radiotherapy, although these results were not statistically significant. However, severe CNS bleeding was considerably more prevalent in patients receiving anticoagulation (8.2% with anticoagulation vs 0.6% without anticoagulation; p=0.001).

One new meta-analysis[^27] since the 2013 CPGs assessed LMWH, unfractionated heparin, and mechanical prophylaxis in 1558 patients who underwent craniotomy. Similar to earlier studies, the use of prophylaxis in patients with neuro-oncological conditions undergoing surgery reduced the occurrence of VTE without increasing bleeding risk (OR 0.24, 95% CI 0.13–0.44; p=0.001). Use of intermittent pneumatic compression devices and LMWH further reduced the VTE occurrence compared with mechanical compression alone (OR 0.57, 95% CI 0.39–0.82; p=0.002). The addition of LMWH was associated with a non-significant increase in major bleeding.

**Thrombocytopenia**

Since the 2013 CPGs, one prospective study[^28] has assessed low-dose dalteparin (100 U/kg daily for 6 months) in 93 patients with thrombocytopenia versus a standard dose (200 U/kg daily for 1 month, followed by 150 U/kg daily for 5 months) in patients with mild to no thrombocytopenia. The proportions of patients with residual VTE, VTE recurrence, and overall bleeding were similar between groups. In a second prospective study[^29] (24401 patients), the incidence of thrombocytopenia was significantly greater with unfractionated heparin (1.4%) than with LMWH (0.5%). Another retrospective study[^30] reported outcomes associated with concomitant VTE and thrombocytopenia in 74 patients with inoperable, advanced pancreatic cancer receiving first-line chemotherapy. Standard anticoagulation significantly reduced the occurrence of VTE (OR 0.13, 95% CI 0.03–0.58) without increasing bleeds, but this reduction was not observed with reduced anticoagulation doses or when administered for less than 3 months.

**Renal failure**

One prospective study[^31] investigated the impact of renal insufficiency on the safety and efficacy of anticoagulant therapy by comparing the risks of recurrent VTE and bleeding in 1279 patients with cancer with and without chronic kidney disease. Risk of major bleeds and fatal bleeds increased with the stage of chronic kidney disease.

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**Panel 5: VTE treatment in unique situations**

**International Advisory Panel ranking: 8.46 out of 9.00**

1. A brain tumour per se is not a contraindication for anticoagulation for established venous thromboembolism (VTE; grade 2C).
2. For the treatment of established VTE in patients with cancer with a brain tumour, we prefer low-molecular-weight heparin (LMWH; guidance).
3. We recommend the use of LMWH or unfractionated heparin (UFH) started postoperatively for the prevention of VTE in patients with cancer undergoing neurosurgery (grade 1A).
4. Primary prophylaxis of VTE in medically treated patients with cancer and with brain tumours who are not undergoing neurosurgery is not recommended (grade 1B).
5. In the presence of severe renal failure (creatinine clearance <30 mL/min), we suggest using UFH followed by early vitamin K antagonists (possible from day 1) or LMWH adjusted to anti-Xa level for the treatment of established VTE (guidance, in the absence of data and an unknown balance between desirable and undesirable effects).
6. In patients with severe renal failure (creatinine clearance <30 mL/min), an external compression device can be applied, and pharmacological prophylaxis should be considered on a case-by-case basis; in patients with severe renal failure (creatinine clearance <30 mL/min), UFH can be used on a case-by-case basis (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the level of VTE risk).
7. In patients with cancer and thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is >50 g/L and bleeding is not evident; for patients with a platelet count <50 g/L, decisions on treatment and dose should be made on a case-by-case basis with the utmost caution (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk vs VTE risk).
8. In patients with cancer with mild thrombocytopenia, a platelet count >80 g/L, pharmacological prophylaxis might be used; if the platelet count is <80 g/L, pharmacological prophylaxis should only be considered on a case-by-case basis and careful monitoring is recommended (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk vs VTE risk).
9. In pregnant patients with cancer, standard treatment for established VTE and standard prophylaxis should be implemented (guidance, in the absence of data and based on the contraindication of vitamin K antagonists during pregnancy).
Conclusion

Most new data from patients with cancer address VTE prophylaxis with LMWH and the effects of DOACs in VTE treatment. LMWH for the treatment and management of established VTE in patients with cancer is well demonstrated, with strong evidence for at least a 3-month treatment duration. Primary thromboprophylaxis with LMWH is also well defined in cancer surgery. The evidence is less clear in medically treated patients with cancer, particularly those receiving ambulatory systemic anticancer therapy. Trials assessing anticoagulants in this population need to be stratified according to VTE and bleeding risks, which vary widely across cancer types and patients. Analysis of patients with cancer from large pivotal trials (containing 169–597 patients) suggest that DOACs are non-inferior to VKAs in the treatment of VTE in this population. Direct data on the safety and efficacy of DOACs in cancer are missing, with the need for dose-finding studies and more research into potential anticancer drug interactions. More than 35 clinical trials are underway to compare DOACs with LMWH.

Declaration of interests

DF was a subinvestigator in the Apex study with Portola, and reports non-financial support from LEO Pharma, Aspen Pharmacare, and Pfizer, outside the submitted work. HB reports grants and personal fees from the Thrombosis Research Institute (London), and personal fees from Bayer Pharmaceuticals, and Sanofi-Aventis, outside the submitted work. BB reports personal fees from Sanofi, Pfizer, ROVI Laboratories, Daiichi Sankyo, Bayer Pharmaceuticals, and Aspen Pharmacare, outside the submitted work. FC reports personal fees from Bayer Pharmaceuticals, non-financial support from LEO Pharma and Aspen Pharmacare, outside the submitted work. PD reports personal fees from a pooled funding source (Bayer Pharmaceuticals, Daiichi Sankyo, LEO Pharma, Aspen Pharmacare, and Celgene) and from Aspen Pharmacare and LEO Pharma, outside the submitted work. AAK reports personal fees and non-financial support from Janssen, LEO Pharma, Sanofi, Pfizer, and Angiodynamics, and personal fees from Bayer Pharmaceuticals, Roche, Daiichi Sankyo, and Boehringer Ingelheim, outside the submitted work. IP reports personal fees from Bayer Pharmaceuticals, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer, outside the submitted work. JD reports grants and personal fees from Boehringer Ingelheim, and personal fees from Janssen, Pfizer, Bayer Pharmaceuticals, Bristol-Myers Squibb, Sanofi, and Daiichi Sankyo, outside the submitted work. AK reports grants and personal fees from Bayer Pharmaceuticals, and personal fees from Boehringer Ingelheim, Daiichi Sankyo, and Pfizer, outside the submitted work. SS declares no competing interests.

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References


