Final Report
Dec. 31, 2020

A systematic review of the beneficial and harmful effects and cost-effectiveness of LMWHs and DOACs for the treatment of venous thromboembolism (VTE) and secondary prophylaxis in cancer patients

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Executive Summary

Background

Cancer is well recognized as a significant risk factor in the development of venous thromboembolism (VTE), and VTE is an important cause of morbidity in patients with cancer. (1) Cancer patients have a fourfold increase in the risk of VTE compared with the general population and VTE is the second most common cause of death in cancer patients, after death due to cancer progression. (2) This has led to considerable clinical research into finding effective and safe treatments for VTE in cancer patients; and large randomized controlled trials (RCTs) have been completed with vitamin K antagonists (VKAs), lowmolecular weight heparins (LMWHs) and, more recently, with direct oral anticoagulants (DOACs).

Warfarin is the prototypical VKA, and it is the only agent in this drug class that remains clinically available in Canada. Warfarin interferes with the synthesis of the following clotting factors in the liver: Factors II, VII, IX and X. LMWHs are produced by chemical or enzymatic breakdown of unfractionated heparin. There are four marketed LMWHs in Canada (dalteparin, enoxaparin, nadroparin, and tinzaparin), and each exerts its anticoagulant effect through selective inhibition of Factor Xa. DOACs exert a direct anticoagulant effect, with apixaban, edoxaban, and rivaroxaban working as direct inhibitors of Factor Xa, while dabigatran is a direct thrombin inhibitor.

There is much variation in the coverage of antithrombotics in cancer-associated VTE across provincial drug programs. The purpose of this report is to provide a review of the clinical and cost-effectiveness published literature to inform drug coverage decisions. The clinical review includes the treatment of cancer-associated VTE and the secondary prophylaxis of cancer-associated VTE. Section A of this report deals with the review of the clinical evidence, while Section B addresses the cost-effectiveness evidence.

SECTION A – CLINICAL EVIDENCE REVIEW

1. Objectives

To conduct a systematic review of the published clinical evidence from active-comparator trials in the treatment of cancer-associated VTE and the secondary prophylaxis of cancer-associated VTE, defined as therapy beyond the initial six months of treatment. The two clinical research questions addressed by this report are shown below.

1. A systematic review of the beneficial and harmful effects of LMWHs and DOACs for the treatment of VTE (DVT, PE) in cancer patients	
P (Population)	Adult cancer patient for treatment of VTE.
I (Intervention)	LMWH [originator and biosimilar] (dalteparin, enoxaparin, nadroparin, and tinzaparin); DOAC (apixaban, rivaroxaban, dabigatran, edoxaban).
C (Comparator)	LMWH vs. VKA, DOAC vs. VKA, LMWH vs. LMWH, LMWH vs. DOAC, DOAC vs. DOAC, LMWH originator vs. LMWH biosimilar.
O (Outcome)	Primary outcome includes documented recurrent VTE (DVT and/or PE). Secondary outcome includes clinical bleeding (major bleeding and any bleeding), mortality (VTE specific and all-cause), and HrQOL. Subgroup analysis includes analyzing the difference in primary and secondary outcomes with different cancer types and ECOG score, as well as reporting the INR score in VKA group.
2. A systematic review of the beneficial and harmful effects of LMWHs and DOACs for the secondary prophylaxis (treatment duration $\geq$ 6 months) of VTE (DVT, PE) in cancer patients	
P (Population)	Adult cancer patients for the secondary prophylaxis of VTE (where secondary prophylaxis is anticoagulant therapy continued after resolution of a first VTE event).
I (Intervention)	LMWH [originator and biosimilar] (dalteparin, enoxaparin, nadroparin, and tinzaparin) and DOAC (apixaban, dabigatran, edoxaban, and rivaroxaban).
C (Comparator)	LMWH vs. VKA, DOAC vs. VKA, LMWH vs. LMWH, LMWH vs. DOAC, DOAC vs. DOAC, LMWH originator vs. LMWH biosimilar.
O (Outcome)	Primary outcome includes documented recurrent VTE (DVT and/or PE). Secondary outcome include clinically bleeding (major bleeding and any bleeding), mortality (VTE specific and all-cause) and HrQOL. Subgroup analysis include analyzing differences in primary and secondary outcomes with various types of cancer, active cancer (include metastasis) or currently on chemotherapy, and ECOG score, as well as reporting the INR score in VKA group.

2. Methods

A systematic review from 2018 was used as the reference document for the literature search as it was a recent Canadian-based investigation that used a robust and transparent search strategy that could be easily reproduced and updated. Their search included the expected standard for a comprehensive yet reasonably specific search strategy, with terms for patient populations, disease, and headings and supplementary concept terms for individual drugs and drug classes. This review identified seven active-comparator anticoagulant trials in cancer-associated VTE, which were published between 2002 and 2018. ReVue replicated this search strategy from January 1, 2018, to June 7, 2020, to identify subsequent relevant RCTs, systematic reviews and meta-analyses of active comparator trials involving VKAs, LMWHs, and DOACs. Multiple search strategies were executed across the PubMed, EMBASE and Cochrane databases.

The abstracts of articles identified were independently reviewed by two individuals to determine if they met the eligibility criteria. Any disagreement on the initial review was resolved by discussion until a consensus was reached. The full text of studies meeting the eligibility criteria was retrieved for further review.

Meta-analyses were specifically reviewed to determine if they used indirect comparison methodology to compare the effects of VKAs, LMWHs, and DOACs on the outcomes of interest.

3. Results

3.1. Treatment of VTE in cancer patients

3.1.1. Literature search results

The literature search identified a total of 1,235 records. After removing duplicates, this number was reduced to 964 records. On review of the abstracts, 809 records were removed from the list. The final list of included citations 39 comprised of 31 systematic reviews and/or meta-analyses, five publications from four unique RCTs and three cost-effectiveness studies. Including the results of the systematic review published in 2018, ReVue identified nine head-to-head RCTs to inform the review.

The identification of the cost-effectiveness studies led to the request that a separate search be completed for additional cost-effectiveness studies; this is fully described in the cost-effectiveness section (Section B) of this report.

3.1.2. Comparison of VKAs vs. LMWHs

Five RCTs in cancer patients have compared warfarin with an LMWH (two with each of enoxaparin and tinzaparin and one with dalteparin). These trials are individually referred to as the CANTHANOX, CLOT, ONCENOX, LITE, and CATCH trials and

were published between 2002 and 2015. They have been included in many of the systematic reviews and/or meta-analyses identified by the literature search.

One of the five RCTs (CLOT trial) reported statistically improved rates of recurrent VTE with dalteparin compared with a VKA, and the other four reported non-statistically significant reductions in recurrent VTE with an LMWH compared with a VKA. Meta-analyses and network meta-analyses of these and other RCTs consistently report lower rates of VTE recurrence with LMWH as a class when compared with a VKA.

None of five RCTs reported statistically significant differences in the rate of major bleeding between dalteparin and a VKA, and one of the RCTs (CATCH trial) reported a lower rate of clinically relevant non-major bleeding (CRNMB) with tinzaparin compared with a VKA. Meta-analyses and network meta-analyses have reported no significant difference between LMWHs and VKAs with respect to bleeding complications.

Overall mortality was similar in patients receiving an LMWH or a VKA in the five RCTs and similar results are reported by meta-analyses and network meta-analyses. The large majority of deaths in the RCTs are attributable to progression of the underlying cancer.

There have been no studies comparing VKAs with LMWHs that have evaluated the impact of these treatments on quality of life (QoL).

ReVue did not find any subgroup analyses of the relative effectiveness or safety of LMWHs versus VKAs based on cancer type or ECOG (or other performance status) score in either individual RCTs or meta-analyses.

There was variable reporting on the time within the therapeutic INR range of 2.0 to 3.0 in the RCTs involving warfarin in cancer-associated VTE. There is inconclusive evidence regarding the impact of the time within the therapeutic range on the relative effectiveness of warfarin compared with LMWHs and whether this information is relevant to the real-world utilization of warfarin in cancer-associated VTE.

3.1.3. Comparison of LMWHs vs. DOACs

The literature search identified four unique RCTs comparing a DOAC with dalteparin: the Hokusai-VTE, SELECT-D, ADAM-VTE and Caravaggio trials. Two of the trials evaluated apixaban (ADAM-VTE and Caravaggio), and one each evaluated rivaroxaban (SELECT-D) and edoxaban (Hokusai-VTE). ReVue also identified three meta-analyses and one network meta-analysis that included data from the four RCTs comparing a DOAC with dalteparin.

Two RCTs (SELECT-D, Caravaggio) reported that a DOAC (rivaroxaban and apixaban) was more effective than dalteparin in reducing recurrent VTE and in the other two trials there were non-significant trends in this direction. Meta-analyses of all patients inthe four RCTs reported a statistically significant 38% relative reduction in VTE recurrence with the DOAC class compared with dalteparin.

One of the four RCTs reported that edoxaban was associated with a higher rate of major bleeding when compared with dalteparin and another RCT reported a higher rate of CRNMB with rivaroxaban compared with dalteparin. All of the meta-analyses and the network meta-analysis reported no statistically significant differences in the rate of major bleeding with the DOAC class compared with dalteparin while two of themeta-analyses reported a higher rate of CRNMB with DOACs compared with dalteparin. The source of the increased bleeding with DOACs versus LMWHs appears to be primarily related to GI and GU bleeding. Bleeding associated with DOACs also appears to be higher in patients with underlying GI cancer.

There were no significant differences in all-cause mortality reported in any of the RCTs nor in the meta-analyses. Three of the four RCTs (Hokusai-VTE, ADAM-VTE and Caravaggio) reported on VTE-related mortality, which was infrequent, and no significant differences were found between DOACs and LMWHs.

One RCT (ADAM-VTE) included an assessment of the effect of a DOAC vs. an LMWH on quality of life, although this was not listed as either a primary or secondary outcome of the study. In general, apixaban was associated with better outcomes across the 13 measures on a quality of life scale in this trial.

Treatment differences between a DOAC and dalteparin are relatively consistent across different types of cancer and patient performance status.

3.1.4. Comparison of DOACs vs. VKAs

There have been no RCTs comparing DOACs with VKAs in patients with cancer. The best evidence that allows for a comparison of these two drug classes comes from a network meta-analysis of trials, which is summarized below.

- DOAC use was associated with a significant reduction in recurrent VTE when compared with VKAs.
- DOAC use was not associated with any difference in the rate of major bleeding nor in the rate of CRNMB when compared with VKAs.
- There is no evidence of a difference between DOACs and VKAs on overall mortality.
- There is no information comparing the quality of life of patients treated with DOACs versus VKAs in cancer-associated VTE.

3.1.5. Comparison of individual LMWHs

There have been no RCTs comparing individual LMWHs with each other in the treatment of VTE in cancer patients. A meta-analysis that reported on the effect size of individual LMWHs versus VKAs on the outcome of recurrent VTE shows overlapping confidence intervals and it is unlikely that an indirect comparison or network meta-analysis would be able to discern any significant differences between the individual LMWHs.

3.1.6. Comparison of individual DOACs

There have been no head-to-head RCTs comparing individual DOACs. Results from two network meta-analyses reporting on the treatment effect of individual DOACs do not provide evidence that any one DOAC is superior to another.

3.1.7 Conclusion

Based on the information from RCTs, meta-analysis and network meta-analyses, the following conclusions can be drawn.

- There is no evidence from RCTs that VKAs are superior to LMWHs. One of five RCTs reported that an LMWH was superior to warfarin with respect to recurrent VTE, and another RCT reported a lower rate of CRNMB with an LMWH vs. a VKA. Meta-analyses consistently report that LMWHs are superior to VKAs with respect to recurrent VTE with no difference in the rates of bleeding complications.
- Two of four RCTs comparing a DOAC with dalteparin report that DOACs are associated with a lower rate of VTE recurrence. However, one RCT reported that a DOAC was associated with a higher rate of major bleeding, and another reported a higher rate of CRNMB with a DOAC. Meta-analysis and network meta-analyses support the superiority of DOACs versus LMWHs on VTE recurrence, with no significant differences in bleeding complications.
- There have been no direct comparisons between a DOAC and a VKA, although network meta-analyses report that DOACs are superior on VTE recurrence, with no difference in bleeding complications.
- There is insufficient evidence that any of the antithrombotic drug classes differs from another on mortality or quality of life.
- There is no evidence that any one LMWH is superior to another; nor is there any evidence that one DOAC is superior to another.

3.2. Secondary prophylaxis of VTE in cancer patients

3.2.1. Literature search results

The evidence for extending anticoagulation beyond six months in patients with cancer-associated VTE is very limited. A placebo-controlled trial of an antithrombotic agent in patients who had previously completed a treatment course for cancer-associated VTE would be helpful in clarifying the effectiveness and safety of such therapy. However, there have been no placebo-controlled trials in patients with cancer-associated VTE who have completed an initial six-month course of therapy.

The majority RCTs evaluating anticoagulant therapy in cancer-associated VTE had duration of therapy of three to six months. ReVue identified three prospective trials that evaluated therapy beyond six months, the DALTECAN, TiCAT and Hokusai-VTE cancer studies. The latter was an RCT comparing edoxaban with dalteparin with a

duration of 12 months while DALTECAN and TiCAT were prospective cohort studies, each with a primary objective to evaluate the safety of dalteparin and tinzaparin, respectively, for up to 12 months of therapy. These cohort studies lacked a comparison group, and their results do not provide evidence of their comparative safety or efficacy.

Additionally, ReVue identified a meta-analysis comparing DOACs with LMWHs that performed a subgroup analysis on the relative risk of recurrent VTE and major bleeding at three, six, and 12 months' duration of therapy.

3.2.2. Outcome: VTE recurrence

The incidence of VTE recurrence in both the DALTECAN and TiCAT studies were higher during the first six months of therapy compared with months seven to 12 of therapy. In DALTECAN, VTE occurred in 4.1% of subjects over the seven-to-12-month period. In TiCAT, the risk was 0.6% per patient-month. The Hokusai-VTE cancer trial did not report a difference in VTE recurrence between edoxaban and dalteparin and no conclusion can be drawn regarding the relative effectiveness of either of these agents during months six to 12 of therapy. All of these trials reported significant patient withdrawals over the 12 months of therapy and this limits interpretation of the data.

The meta-analysis reported relatively consistent differences in the rate of VTE recurrence between a DOAC and an LMWH for the subgroups of three, six and 12 months of therapy.

Overall, there is insufficient evidence regarding the relative effectiveness of continuing antithrombotic therapy beyond six months.

3.2.3. Outcome: Bleeding complications

The primary outcome of the DALTECAN study was major bleeding at months seven to 12 of therapy and this occurred in 0.7% of subjects compared with an incidence of major bleeding of 1.7% within the first six months of therapy. The primary outcome of the TiCAT study was a composite of major bleeding and CRNMB and this occurred ata rate of 0.9% patient-month during the first six months versus 0.6% patient-month during months seven to 12.

The Hokusai-VTE cancer trial reported a higher rate of bleeding with edoxaban compared with dalteparin and this difference appeared to be maintained during months seven to 12 of the trial. However, this requires careful interpretation given the high number of patient withdrawals over this period.

The meta-analysis reported no differences in the rates of major bleeding betweenDOACs and LMWHs for the subgroups of three, six, and 12 months of therapy.

3.2.4 Conclusion

A placebo-controlled trial of an antithrombotic agent in patients who had previously completed a treatment course for cancer-associated VTE would be helpful in clarifying the effectiveness and safety of such therapy. However, there have been no placebo-controlled trials in patients with cancer-associated VTE who have completed an initial six-month course of antithrombotic therapy. Limited evidence from prospective studies of 12 months' duration suggests that the risk of bleeding complications with DOACs and LMWHs are relatively lower during months seven to 12 when compared with the first six months of therapy, but there is insufficient information regarding their effectiveness. Therefore, evidence for extending anticoagulation beyond six months in patients with cancer-associated VTE is very limited.

SECTION B – COST-EFFECTIVENESS REVIEW

1. Objective

To identify, analyze and synthesize published information on the relative cost-effectiveness of antithrombotic agents and classes in cancer-associated VTE. As this information will inform public drug funding decisions in the Canadian context, literature from Canada or jurisdictions with similar publicly-funded drug programs are prioritized.

2. Methods

A literature search for relevant studies was conducted on July 6, 2020. Databases included in the search were Ovid Medline, Embase and the grey literature and articles were specifically screened for publications from Canada, Australia, the European Union, New Zealand, and the United Kingdom.

The abstracts of articles identified were independently reviewed by two individuals to determine if they met the eligibility criteria. Any disagreement on the initial review was resolved by discussion until a consensus was reached. The full text of studies meeting the eligibility criteria was retrieved for further review.

3. Results

The search strategy outlined in Appendix 5 identified 40 publications of interest. On further review, this number was reduced to five publications that qualified for a review of the full paper.

Four of the studies had significant limitations:

- One did not include DOACs in their economic model;
- Two (by the same author group) had inherent biases in that they were funded by the pharmaceutical manufacturer of dalteparin and the authors included employees of the manufacturer;
- One was from the perspective of a US third-party payer.

The remaining publication was a clinical review and economic evaluation of anticoagulants in VTE published by the National Institute for Health and Care Excellence (NICE). They developed a de novo economic model for adults with a confirmed VTE and a subgroup analysis was performed in people with cancer. The methodology used by NICE included a network meta-analysis of 11 active-comparator RCTs of anticoagulants in cancer-associated VTE. VKAs and LMWHs were each considered as a class, while DOACs were considered individually. Separate results were produced for patients with deep vein thrombosis (DVT) and for those with pulmonary embolus (PE).

Their model reported that, when one QALY is valued at £20,000, apixaban had a 49% probability of being the preferred choice, while rivaroxaban and unfractionated heparin/VKA had probabilities of 23% and 16% of being preferred, respectively. For patients with a PE, apixaban had a 51% probability of being the preferred treatment option, while rivaroxaban and unfractionated heparin/VKA have probabilities of 26% and 13%, respectively. For both DVT and PE, LMWH had a 0% chance of being cost-effective, due to its higher acquisition cost.

The NICE Committee recommended that a DOAC be considered for the treatment of cancer-associated VTE but they did not recommend one DOAC over another. Furthermore, they recommended that if a DOAC is deemed to be unsuitable, an LMWH alone, or an LMWH followed by warfarin should be considered.

4. Conclusion

Despite a relative lack of robust economic evaluations and uncertainty regarding clinical effectiveness and safety inputs, it appears that a DOAC is a cost-effective option for the treatment of cancer-associated VTE. At current drug acquisition costs, it is unlikely that LMWHs are a cost-effective option.

DETAILED REPORT

Background

Cancer is well recognized as a significant risk factor in the development of venous thromboembolism (VTE), and VTE is an important cause of morbidity in patients with cancer. (1) Cancer patients have a fourfold increase in the risk of VTE in comparison with the general population; and VTE is the second most common cause of death in cancer patients, afterdeath due to cancer progression. (2) This has led to considerable clinical research into finding effective and safe treatments for VTE in cancer patients, and large randomized controlled trials (RCTs) have been completed with vitamin K antagonists (VKA), low molecular weight heparins (LMWHs) and, more recently, with direct oral anticoagulants (DOACs).

Warfarin is the prototypical vitamin K antagonist, and it is the only agent in this drug class that remains clinically available in Canada. Warfarin interferes with the synthesis of the following clotting factors in the liver: Factors II, VII, IX, and X. LMWHs are produced by chemical or enzymatic breakdown of unfractionated heparin. There are four marketed LMWHs in Canada (dalteparin, enoxaparin, nadroparin, and tinzaparin), all of which exert their anticoagulant effect through selective inhibition of Factor Xa. DOACs exert a direct anticoagulant effect, with apixaban, edoxaban, and rivaroxaban working as direct inhibitors of Factor Xa, while dabigatran is a direct thrombin inhibitor.

As shown in the table in Appendix 1, there is much variation in the coverage of antithrombotics in cancer-associated VTE across provincial drug programs. Currently, BC provides warfarin as first-line therapy for cancer-associated VTE and allows for special authorization use of dalteparin and tinzaparin in select patients. In order to ensure that coverage of anticoagulants in cancer-associated VTE is consistent with clinical evidence, a review of the published clinical evidence and cost-effectiveness of various anticoagulants was commissioned by the Therapeutic Assessment and Access Branch in BC.

The purpose of this report is to provide a review of the clinical and cost-effectiveness published literature to inform drug coverage decisions. The clinical review includes the treatment of cancer-associated VTE and the secondary prophylaxis of cancer-associated VTE, which is considered to be therapy beyond the initial six months of treatment. Section A of this report deals with the review of the clinical evidence, while Section B addresses the cost-effectiveness evidence.

SECTION C – CLINICAL EVIDENCE REVIEW

1. Objectives

Two clinical research questions were originally developed in February 2020 and finalized in April 2020. The final versions are shown below.

1. A systematic review of the beneficial and harmful effects of LMWHs and DOACs for the treatment of VTE (DVT, PE) in cancer patients	
P (Population)	Adult cancer patient for treatment of VTE.
I (Intervention)	LMWHs [originator and biosimilar] (dalteparin, enoxaparin, nadroparin and tinzaparin); DOACs (apixaban, rivaroxaban, dabigatran, edoxaban).
C (Comparator)	LMWH vs. VKA, DOACs vs. VKA, LMWH vs. LMWH, LMWH vs. DOACs, DOACs vs. DOACs, LMWH originator vs. LMWH biosimilar.
O (Outcome)	Primary outcome includes documented recurrent VTE (DVT and/or PE). Secondary outcome includes clinical bleeding (major bleeding and any bleeding), mortality (VTE specific and all-cause) and HrQOL. Subgroup analysis include analyzing the difference in primary and secondary outcomes with different cancer types and ECOG score, as well as reporting the INR score in VKA group.
2. A systematic review of the beneficial and harmful effects of LMWHs and DOACs for the secondary prophylaxis (treatment duration ≥ 6 months) of VTE (DVT, PE) in cancer patients	
P (Population)	Adult cancer patients for the secondary prophylaxis of VTE (where secondary prophylaxis is anticoagulant therapy continued after resolution of a first VTE event).
I (Intervention)	LMWHs [originator and biosimilar] (dalteparin, enoxaparin, nadroparin and tinzaparin) and DOACs (apixaban, dabigatran, edoxaban and rivaroxaban).
C (Comparator)	LMWH vs. VKA, DOACs vs. VKA, LMWH vs. LMWH, LMWH vs. DOACs, DOACs vs. DOACs, LMWH originator vs. LMWH biosimilar.
O (Outcome)	Primary outcome includes documented recurrent VTE (DVT and/or PE). Secondary outcome include clinically bleeding (major bleeding and any bleeding), mortality (VTE specific and all-cause) and HrQOL. Subgroup analysis include analyzing difference in primary and secondary outcomes with different cancer types, active cancer (include metastasis) or currently on chemotherapy, and ECOG score, as well as reporting the INR score in VKA group.

2. Methods

A comprehensive search of the literature is fundamental for systematic reviews. As the search strategy and findings of previous published systematic reviews may provide comprehensive strategies, the literature searches in published systematic reviews were compared, including the reviews by Key et al. (1) and Carrier et al. (2) There was agreement that the systematic review by Carrier et al. (2), was to be used as the reference document for the literature search in that it was a recent Canadian-based investigation that used a robust and transparent search strategy that could be easily reproduced and updated. Their search included the expected standard for a comprehensive yet reasonably specific search strategy, with terms for patient populations, disease, and headings and supplementary concept termsfor individual drugs and drug classes. Their search identified seven active-comparator anticoagulant trials in cancer-associated VTE, which were published between 2002 and 2018.ReVue replicated their search strategy from January 1, 2018, to June 7, 2020, to identify subsequent relevant RCTs, systematic reviews and meta-analyses of active comparator trialsinvolving VKAs, LMWHs, and DOACs. To further ensure a comprehensive yield of citations from PubMed, EMBASE and Cochrane databases, multiple search strategies were executed. In particular, the search strategies used by authors of recent systematic reviews and guidelines (1, 2) were used for PubMed. The searches overlapped the dates of the searches in these publications to account for the possibility of late entries of citations in the databases. The full search strategy is shown in Appendix 2.

The abstracts of articles identified by the search strategy were independently reviewed by two individuals to determine if they met the eligibility criteria. Any disagreement on the initial review was resolved by discussion until a consensus was reached. The full text of studies meeting the eligibility criteria was retrieved for further review.

Meta-analyses were specifically reviewed to determine if they used indirect comparison methodology to compare the effects of VKAs, LMWHs, and DOACs on the outcomesof interest.

Clinical practice guidelines were not included as part of the literature search and review, but at the client's request selected guidelines are summarized in Appendix 3.

3. Results

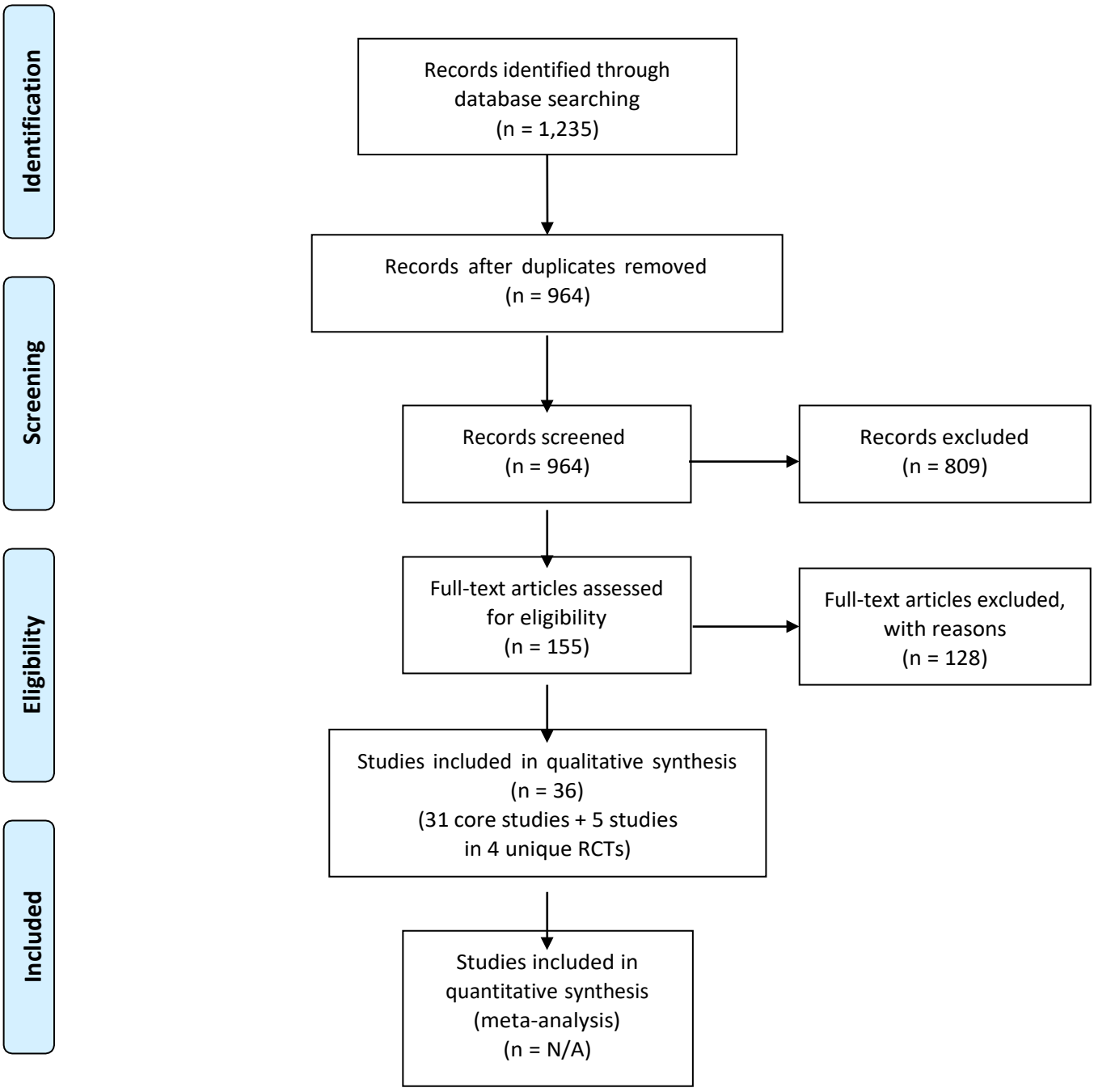
3.1. Literature search results

As shown on the following PRISMA Flow Diagram, a total of 1,235 records were identified. After removing duplicates this number was reduced to 964 records. These were in turn examined and 809 records were removed from the list. The reasons(s) exclusion were:

- They excluded or had only a minimal number of, cancer patients;
- They were already included in the Carrier systematic review;
- They were not relevant to the specific drugs and conditions in the PICO;
- They were not published RCTs.

After the initial search, 23 studies along with four RCTs were identified. Following a number of in-depth conversations with the team at the BC Ministry of Health, additional studies were added bringing the total to 36 studies, comprised of 31 systematic reviews and/or meta-analyses and five publications from four unique RCTs. Separately, three cost- effectiveness studies were flagged for review. Further discussion with the team at the BC Ministry of Health led to the request that a separate search be completed for additional cost-effectiveness studies; this is fully described in the cost-effectiveness section (Section B) ofthis report.

PRISMA Flow Diagram – DOACs Project



A complete list of the 36 studies identified in the clinical review can be found in Appendix 3. Two additional head-to-head RCTs published in 2020, each comparing apixaban with dalteparin, were identified that were not included in the review by Carrier et al. (3, 4) Additionally, a large number of systematic reviews and meta analyses have been published since January 2018 and these are also used to address the research questions (see Appendix 4).

Appendix 5 provides a network diagram of the nine head-to-head RCTs that inform the review.

3.2. Research Question 1. A systematic review of the beneficial and harmful effects of LMWHs and DOACs for the treatment of VTE (DVT, PE) in cancer patients

Since the publication of the systematic review by Carrier et al. (2), ReVue identified two additional RCTs published in 2020, each comparing apixaban with dalteparin, were identified to inform this review. (3, 4) Systematic reviews and meta-analyses are selectively used to address the research question (see Appendix 3). The following sections address the evidence comparing each of the drug classes with each other on the outcomes of interest in the review in the following order:

- VKAs vs. LMWHs
- LMWHs vs. DOACs
- VKAs vs. DOACs

3.2.1. Comparison of VKAs vs. LMWHs

3.2.1.1. Summary of studies

Five RCTs in cancer patients have compared a VKA with an LMWH (two with each of enoxaparin and tinzaparin and one with dalteparin). These were published between 2002 and 2015 and have been included in many of the systematic reviews and/or meta-analyses identified by the literature search. These RCTs are summarized in Table 1 on the following page. There have subsequently been many systematic reviews, meta-analyses and network meta-analyses comparing LMWHs as a class with VKAs, each of which included the above five RCTs in addition to RCTs that included cancer patients asa subgroup of a larger population. The results of these are summarized in Table 2 on the following page.

Table 1. Summary of RCTs comparing LMWHs with VKAs in cancer patients

	CANTHANOX (5)	CLOT (6)	ONCENOX (7)	LITE (8)	CATCH (9)
Study drugs	Enoxaparin vs. VKA	Dalteparin vs. VKA	Enoxaparin vs. VKA	Tinzaparin vs. VKA	Tinzaparin vs. VKA
Publication date	2002	2003	2006	2006	2013
Design	Superiority	Superiority	Pilot feasibility trial	Superiority	Superiority
Primary endpoint	Composite of recurrent VTE or major bleed	Recurrent VTE	Feasibility of recruitment	Recurrent VTE	Recurrent VTE
N	138	772	91	200	900
Duration	3 months	6 months	3 months	3 months	6 months
Recurrent VTE	E 3%, VKA 4.2% RR 0.7 (CI 0.12–4.09)	D 9%, VKA 17% RR 0.51 (CI 0.33–0.79) p = 0.002	E 6.6%, VKA 10% RR 0.68 (CI 0.16–2.85)	T 6%, VKA 10% RR 0.44 (CI 0.12–1.02)	T 6.9%, VKA 10.0% RR 0.65 (CI 0.41–1.03) p = 0.07
Major bleed	E 7%, VKA 16% RR 0.44 (CI 0.16–1.19) p = 0.09	D 4%, VKA 6% RR 1.58 (CI 0.78–3.21) p = 0.27	E 9%, VKA 3% RR 3.04 (CI 0.38–24.28)	T 7%, VKA 7% RR 1.0 (CI 0.36–2.75)	T 2.7%, VKA 2.4% RR 1.1 (CI 0.49–2.46) p = 0.77
CRNMB	E 7%, VKA 13% RR 0.59 (0.21–1.67)	NA	E 64%, VKA 57% RR 1.16 (CI 0.79–1.71)	T 20%, VKA 17% RR 1.18 (CI 0.66–2.11)	T 10.9%, VKA 15.3% RR 0.71 (CI 0.51–1.00) p = 0.004
Overall mortality	E 11.9%, VKA 23.9% RR 0.50 (CI 0.23–1.08) p = 0.25	D 39%, VKA 41% RR 0.96 (CI 0.76–1.15) p = 0.53	E 37%, VKA 36% RR 1.01 (CI 0.56–1.84)	T 47%, VKA 47% RR 1.0 (CI 0.75–1.34)	T 33.4%, VKA 30.1% RR 1.09 (CI 0.90–1.32) p = 0.54

D = dalteparin, E = enoxaparin, T = tinzaparin, CRNMB = clinically relevant non-major bleeding, RR = relative risk, CI = 95% confidence interval, NA = not available

Table 2. Summary of meta-analyses comparing LMWHs with VKAs

	Kirkilesis (10)	**Rossel (11)**	**Sobieraj (12)**	**Vedovati (13)**
Type of analysis	MA	NMA	NMA	NMA
# of trials	11	7	7	6
# of patients	2,777	2,095	NR	2,078
Recurrent VTE	0.58 (CI 0.45–0.75)	0.57 (CI 0.44–0.75)	0.64 (CI 0.50–0.81)	0.67 (CI 0.50–0.91)
Major bleed	0.99 (CI 0.67–1.45)	0.71 (CI 0.49–1.04)	0.75 (CI 0.46–1.22)	1.0 (CI 0.62–1.61)
CRNMB	0.88 (CI 0.70–1.12)	0.82 (CI 0.52–1.29)	NR	NR
Overall mortality	0.99 (CI 0.91–1.09)	0.96 (CI 0.83–1.10)	1.02 (CI 0.90–1.15)	NR

MA = meta-analysis, NMA = network meta-analysis, CRNMB = clinically relevant non-major bleeding, NR = not reported

3.2.1.2. Outcome: Recurrent VTE

One of the five RCTs (the CLOT trial) reported statistically improved rates of recurrent VTE with dalteparin compared with a VKA and the other four reported non-statistically significant reductions in recurrent VTE with an LMWH compared with a VKA. (8)

There are some notable differences between these five RCTs. In addition to the long time-frame over which the RCTs were conducted, they also differ in their duration of therapy (three months for CANTHANOX, ONCENOX and LITE versus six months for CLOT and CATCH) and sample size that ranged from 91 for ONCENOX (which was a feasibility pilot study) to 900 for CATCH. While only the CLOT trial reported a statistically significant improvement in recurrent VTE with dalteparin versus a VKA, all five RCTs reported a numerical reduction in recurrent VTE with an LMWH compared with a VKA.

The two largest RCTs comparing an LMWH with a VKA are the CLOT and CATCH trials, and the CLOT trial reported a statistically significant reduction in recurrent VTE with dalteparin versus VKA (warfarin and acenocoumarol were allowed) while the CATCH trial found no significant difference between tinzaparin and warfarin. A more detailed comparison of these two trials is shown in Table 3. Overall, patients enrolled in the CATCH trial appeared to have less advanced underlying cancer as evidenced by a higher proportion of patients with an ECOG score of 0 or 1 and a lower incidence of patients with metastatic disease. Additionally, patients enrolled in the CLOT trial had a higher rate of a history of a previous VTE. While it is unclear if these differences explain the lower rates of recurrent VTE in the tinzaparin and warfarin arms of the CATCH trialcompared with the CLOT trial, it is plausible that it is a contributing factor. Based on published data at the time of study design, the CATCH trial was powered to detect a relative risk reduction in recurrent VTE of 50% with tinzaparin in relation to an assumedrate of recurrent VTE with warfarin of 12.6%. The rate of recurrent VTE observed in CATCH trial was lower than anticipated, and thus it may have been underpowered to detect statistically significant differences in recurrent VTE.

Table 3. Comparison of CLOT and CATCH trials

	CLOT (2003)	CATCH (2013)
Primary outcome	Objectively documented, symptomatic, recurrent deep-vein thrombosis, pulmonary embolism, or both.	Composite of symptomatic DVT, symptomatic non-fatal PE, fatal PE; incidental proximal DVT (popliteal or higher), and incidental proximal PE (segmental arteries or larger).
Mean age	62.5	59.2
ECOG < 2	63%	77%
Metastatic disease	67.3%	54.7%
History of VTE	11.1%	6.3%
Qualifying event		
• DVT alone	68.8%	56.7%
• PE with or without DVT	31.2%	40.7%
VTE outcomes		
• Symptomatic DVT	D 4.2%, VKA 11.0%	T 2.7%, VKA 5.3%
• Symptomatic nonfatal PE	D 2.4%, VKA 2.7%	T 0.7%, VKA 0.4%
• Incidental VTE	Not included	T 0%, VKA 0.4%
• Fatal PE	D 1.5%, VKA 2.1%	T 3.8%, VKA 3.8%

DVT = deep vein thrombosis, PE = pulmonary embolism, ECOG = Eastern Cooperative Oncology Group

As shown in Table 2, meta-analyses and network meta-analyses of these and other RCTs consistently report lower rates of VTE recurrence with LMWH as a class when compared with VKAs.

3.2.1.3. Outcome: Bleeding complications

None of five RCTs reported statistically significant differences in rates of major bleeds between patients treated with an LMWH versus a VKA, and only the CATCH trial reported a lower rate of clinically relevant non-major bleeding (CRNMB) with tinzaparin compared with warfarin. Meta-analyses and network meta-analyses have not found statistically significant differences in rates of major bleeding nor CRNMB with an LMWH versus a VKA.

3.2.1.4. Outcome: Overall mortality

Mortality is relatively high in trials of anticoagulants in the prevention of VTE in cancer patients and, not surprisingly, the large majority of deaths are attributed to progression of the underlying cancer. For example, in the CLOT and CATCH trials death from pulmonary embolus (PE) occurred in 1.8% and 3.8% of all patients respectively, while overall mortality in these trials were 40.0% and 31.7%, respectively. Overall mortality was similar in patients receiving an LMWH or a VKA in the five RCTs and similar results are reported by meta-analyses and network-meta-analysis.

During discussion of an earlier draft of this report, it was noted that the United States Food and Drug Administration (FDA) approval of dalteparin for the prevention of VTE

recurrence in cancer patients was delayed due to concerns regarding a higher death rate amongst patients on-treatment with dalteparin compared with a VKA in the CLOT trial. Subsequent analysis clarified that this difference could be explained by the censoring of patients who died on treatment. More patients with terminal cancer discontinued their VKA treatment for clinical management reasons (e.g., need for blood work for INR monitoring) while relatively more patients receiving dalteparin continued treatment until their death. Additionally, patients in this trial discontinued their study drug if they developed a recurrent VTE and the rate of VTE recurrence in this trial was significantly higher in the VKA arm (17%) than the dalteparin arm (9%). (14) Once this issue was clarified, the FDA approved the use of dalteparin in cancer patients in 2008.

3.2.1.5. Outcome: Quality of life

There have been no studies comparing VKAs with LMWHs that have evaluated the impact of these treatments on quality of life (QoL).

3.2.1.6. Impact of cancer type and performance status

ReVue could not find any subgroup analyses of the relative effectiveness or safety of LMWHs versus VKAs based on cancer type or ECOG (or other performance status) score in either individual RCTs or meta-analyses.

3.2.1.7. Reporting of time in therapeutic range in VKA trials

In the five RCTs involving warfarin in cancer-associated VTE, there was variable reporting on the time within the therapeutic INR range of 2.0 to 3.0:

- Meyer et al. (CANTHANOX trial) reported that patients were within the therapeutic range 41% of the time. (5)
- Lee et al. (CLOT trial) reported a mean (± SD) INR of 2.5 ± 0.75 and using linear interpolation, they estimated that the INR was in the therapeutic range 46% of the time, below the range 30% of the time, and above the range 24% of the time. (6)
- Deitcher et al. (ONCENOX trial) did not report on the INR range though it should be noted there were only 30 patients in the warfarin group in this trial. (7)
- Hull et al. (LITE trial) did not report details on the time within the therapeutic range but did indicate that of 100 patients in the warfarin group, 10 developedrecurrent VTE at three months and one of these patients had an INR of < 2 at thetime of the event. (8)
- Lee et al. (CATCH trial) reported the mean time in the INR therapeutic range was 47.0%. The percentage of time below the therapeutic range was 26.1% and time above the range was 26.9%. (9)

Based on the above, there is inconclusive evidence regarding the impact of the time within the therapeutic range on the relative effectiveness of warfarin compared with LMWHs and whether this information is relevant to the real-world utilization of warfarin in cancer-associated VTE.

3.2.1.8. Summary

One of five RCTs that compared an LMWH with a VKA reported a lower rate ofrecurrent VTE (the CLOT trial with dalteparin), none of the trials reported differences inthe rates of major bleeding, and only the CATCH trial reported a statistically lower rate CRNMB with tinzaparin compared with a VKA. None of the RCTs reported differences in overall mortality between an LMWH and a VKA. Meta-analyses and network meta- analyses of RCTs comparing VKAs with LMWHs indicate that the latter are associated with improved rates of recurrent VTE with no significant difference in the rate ofbleeding complications or overall mortality.

The balance of all evidence from RCTs and meta-analyses supports the superiority of LMWHs over VKAs for the prevention of recurrent VTE in cancer patients.

3.2.2. Comparison of LMWHs vs. DOACs

3.2.2.1. Summary of studies

The literature search identified four unique RCTs comparing a DOAC with dalteparin (3, 4, 15, 16) and one additional trial that reported on a pre-defined endpoint of major bleeding in one (Hokusai-VTE) of the four trials. (17) Two of the trials evaluated apixaban (ADAM-VTE and Caravaggio), and one each evaluated rivaroxaban and edoxaban (SELECT-D and Hokusai-VTE), respectively. A summary of the results of these four RCTs on the endpoints of interest of this review are presented in Table 4.

Table 4. Summary of RCTs comparing DOACs with dalteparin

	Hokusai-VTE cancer (15)	**SELECT-D (16)**	**ADAM-VTE (3)**	**Caravaggio (4)**
Study drugs	Edoxaban vs. dalteparin	Rivaroxaban vs. dalteparin	Apixaban vs. dalteparin	Apixaban vs. dalteparin
Design	Noninferiority	Pilot study for rate of recurrent VTE	Superiority	Noninferiority
Primary endpoint	Composite of recurrent VTE or major bleed	Recurrent VTE	Major bleed	Recurrent VTE
N	1,046	406	287	1,155
Duration	Up to 12 months	6 months	6 months	6 months
Recurrent VTE	E 7.9%, D 11.3% HR 0.71 (CI 0.48–1.06) p = 0.09	R 4%, D 11% HR 0.43 (CI 0.19–0.99)	A 0.7%, D 6.3% HR 0.1 (CI 0.013–0.78) p = 0.028	A 5.6%, D 7.9% HR 0.63 (CI 0.37–1.07) p < 0.001 for noninferiority, p = 0.09 for superiority
Major bleed	E 6.9%, D 4.0% HR 1.77 (CI 1.03–3.04) p = 0.04	R 6%, D 4% HR 1.83 (CI 0.68–4.96)	A 0%, D 1.4% p = 0.138	A 3.8%, D 4.0% HR 0.82 (CI 0.40–1.69) p = 0.60
CRNMB	CRNMB: E 14.6%, D 11.1% HR 1.38 (0.98–1.94)	CRNMB: R 13%, D 4% HR 3.76 (CI 1.63–8.69)	CRNMB: A 6.2%, D 4.2% (NSS)	CRNMB: A 9.0%, D 6.0% HR 1.42 (CI 0.88–2.30)
Overall mortality	E 39.5%, D 36.6% HR 1.12 (CI 0.92–1.37)	R 25%, D 30% (NSS)	A 16%, D 11% p = 0.31	A 23.4%, D 26.4% HR 0.82 (CI 0.62–1.09)
VTE mortality	E 1.1%, D 0.8%	NR	None in either group	A 0.7%, D 0.7% (NSS)
QoL	NR	NR	Overall A sig better than D on an anticoagulant patient satisfaction scale.	NR

A = apixaban, D = dalteparin, E = edoxaban, R = rivaroxaban, CRNMB = clinically relevant non-major bleeding, HR = hazard ratio, CI = 95% confidence interval, QoL = quality of life, NSS = not statistically significant, NR = not reported

Table 5. Meta-analysis studies comparing DOACs with LMWHs*

	Ueyama et al. (18)	Mulder et al. (19)	Giustozza et al. (20) Moik et al. (21)
Type of analysis	NMA	MA	MA
Included drug classes	VKA, LMWH, DOAC	LMWH, DOAC	LMWH, DOAC
Included studies	4 RCTs	4 RCTs	4 RCTs
# of patients	2,894	2,607	2,894
VTE recurrence	RR 0.75 (CI 0.59–0.94)	RR 0.68 (CI 0.39–1.17)	RR 0.62 (CI 0.43–0.91)
Major bleeding	RR 1.11 (CI 0.74–1.68)	RR 1.36 (CI 0.55–3.35)	RR 1.31 (CI 0.83–2.08)
CRNMB	RR 1.28 (CI 0.95–1.72)	RR 1.63 (CI 0.73–3.64)	RR 1.65 (CI 1.19–2.28)
Overall mortality	NR	RR 0.96 (CI 0.68–1.36)	RR 0.99 (CI 0.83–1.18)

CI = 95% confidence interval, CRNMB = clinically relevant non-major bleeding, MA = meta-analysis, NMA = network meta-analysis, NR = not reported , RR = relative risk

* Results presented for comparison of LMWHs vs. DOACs only.

Two of the meta-analyses presented Forest plots of relevant outcomes, reproduced in Figures 1 and 2.

Figure 1. Forest plot of recurrent VTE and major bleeding from Giustozzi et al. (20)

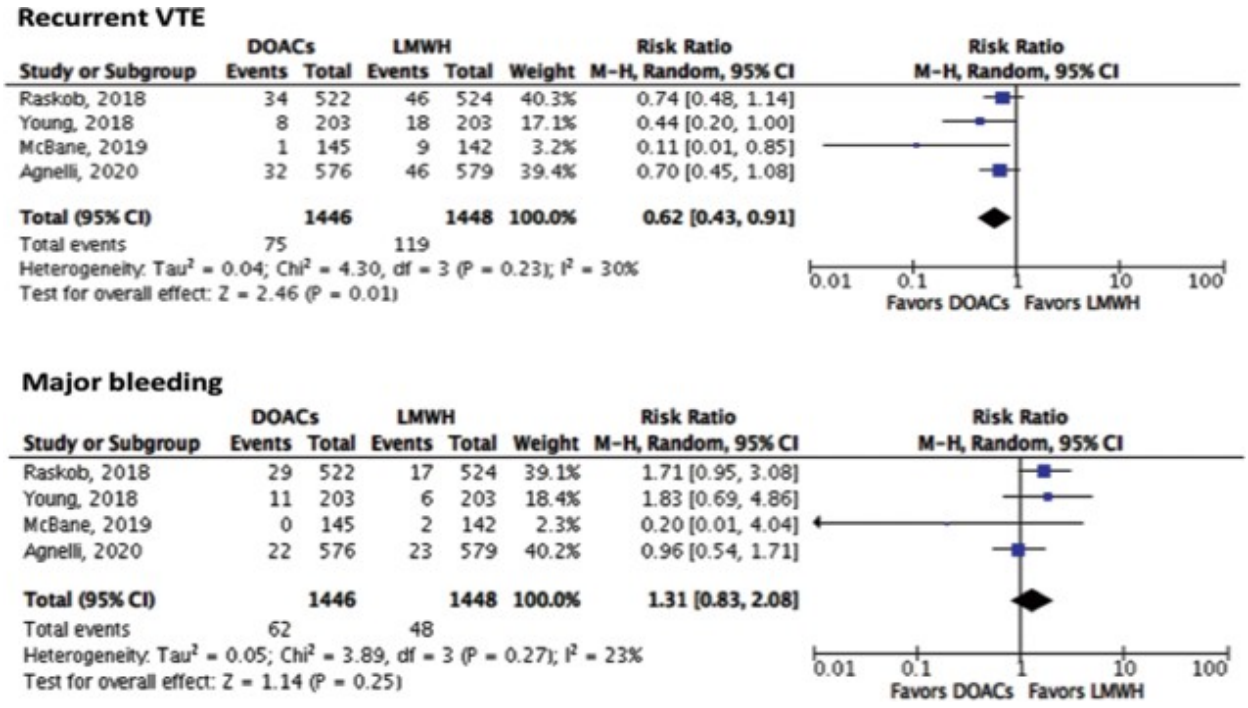
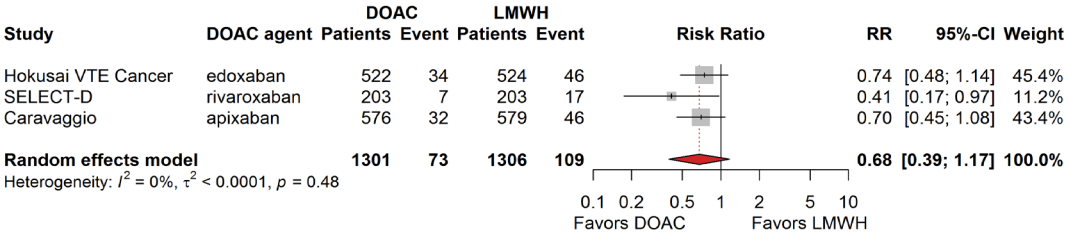
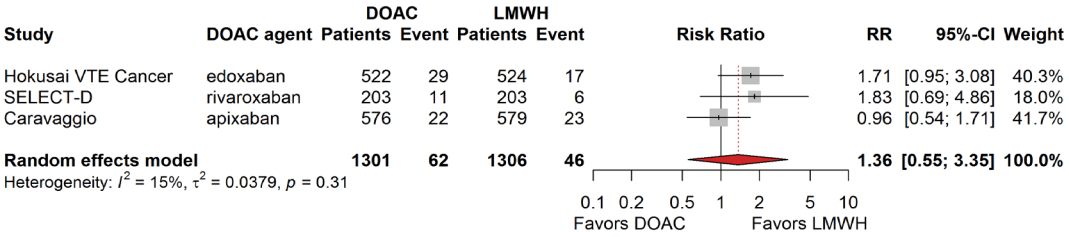


Figure 2. Forest plot of outcomes from Mulder et al. (19)

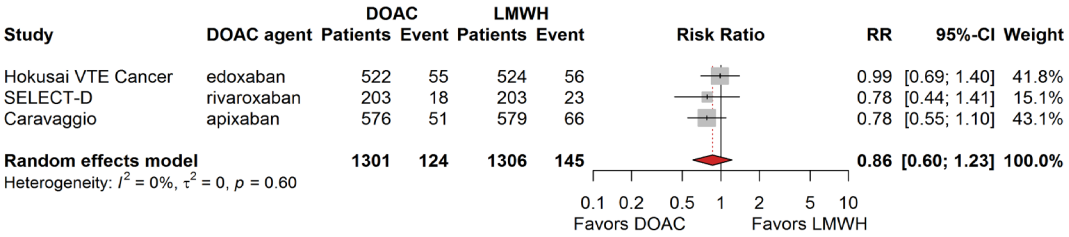
Recurrent VTE



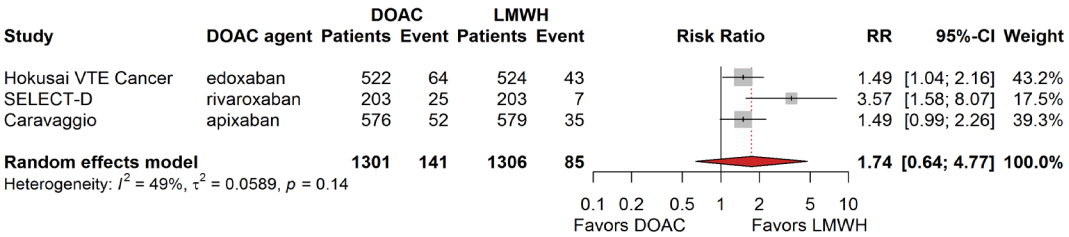
Major bleeding



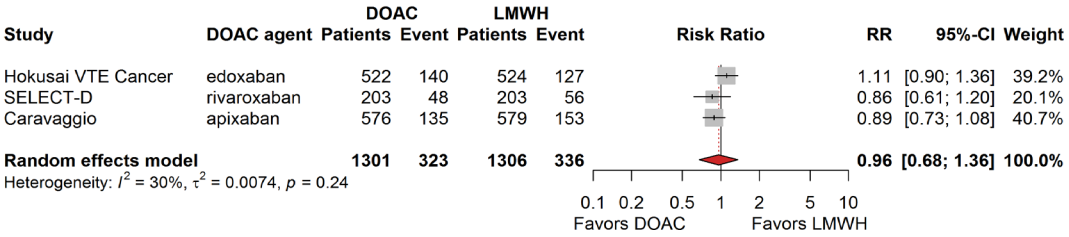
Composite of first major bleeding or recurrent VTE



Clinically relevant non-major bleeding



All-cause mortality



ReVue also identified three meta-analyses and one network meta-analysis that included data from the four RCTs comparing a DOAC with dalteparin. (18–21) Meta-analysis is a well suited approach with these trials as the populations included in the individual RCTs were relatively homogenous: the majority of patients in the trials had active cancer (97–100% of subjects), had metastatic disease (53–68% of subjects) were receiving anticancer treatment at or within four weeks of enrolment (62–74% of subjects) and the ECOG performance scores at enrolment were similar (ECOG 0 in 29–41% of subjects, ECOG 1 in 45–49% of subjects and ECOG 2 in 11–24% of subjects). Additionally, lung and colorectal cancer were the two most common causes of cancer in each of the trials.

The results are shown in Table 5 with two of the studies combined in one column as they reported identical results owing to identical methodology. Results are generally consistent among these four studies, with minor differences in results due to one meta-analysis (18) also including RCTs that identified subgroups of cancer patients, one meta-analysis excluding patients with non-deep vein thrombosis (DVT) VTE (19) and differences in the statistical analyses of the results.

3.2.2.2. Outcome: Recurrent VTE

Two (SELECT-D, ADAM-VTE) of the four RCTs reported that a DOAC (rivaroxaban and apixaban) was more effective than dalteparin in reducing recurrent VTE (3, 16) and in the other two trials there were non-significant trends in this direction. (3, 15) Meta-analyses of all patients in the four RCTs reported a statistically significant 38% reduction in VTE recurrence with the DOAC class compared with dalteparin. (20, 21) Similar results were found by Ueyama et al. using a network meta-analysis approach. (18) In a meta-analysis where patients with non-deep vein thrombosis were excluded, there was no statistically significant difference VTE recurrence between a DOAC and dalteparin. (19)

3.2.2.3. Outcome: Bleeding complications

One (Hokusai-VTE) of the four RCTs reported that edoxaban was associated with a higher rate of major bleeding when compared with dalteparin (15) and another RCT (SELECT-D) reported a higher rate of CRNMB with rivaroxaban compared with dalteparin. (16) All of the meta-analyses and the network meta-analysis reported no statistically significant differences in the rate of major bleeding with the DOAC class compared with dalteparin while two of the meta-analyses reported a higher rate of CRNMB with DOACs compared with dalteparin. (20, 21)

Carrier et al. (2) reported that the increased bleeding reported in the edoxaban and rivaroxaban trials appeared to be primarily gastrointestinal (GI) bleeds and that GI and genitourinary (GU) cancer patients are at a higher risk for bleeding from DOACs.

A further analysis of bleeding events in the edoxaban and dalteparin groups of the Hokusai-VTE cancer trial (15), was published by Kraaijpoel et al. (17) Bleeding events were reviewed by an independent adjudication committee that was unaware which study drug patients received. Of 1,046 patients included in the safety analysis of the

trial, major bleeding occurred in 32 (6.1%) of edoxaban patients and 16 (3.1%) of dalteparin patients (hazard ratio 2.0, 95% CI 1.09–3.66, p = 0.025). GI bleeding accounted for virtually all of this difference in the treatments: 22 patients (4.2%) in the edoxaban group had GI bleeding compared with five patients (1.0%) in the dalteparin group. The risk of major bleeding according to cancer type was also investigated and in patients with GI cancer, there was a higher risk of major bleeding with edoxaban versus dalteparin (12.7 vs. 3.6% respectively; hazard ratio 4.0, 95% CI 1.15–10.6, p = 0.005). GI bleeding was the source of the major bleed in 71.4% of the edoxaban group. There was no indication that GU cancer patients had increased rates of bleeding with edoxaban.

Unfortunately, there has been no similar analysis of bleeding events in the SELECT-D, ADAM-VTE, and Caravaggio trials, and it is difficult to ascertain if the increased rate of major bleeding with edoxaban in the Hokusai-VTE trial compared with the other trials is DOAC specific or trial specific. Given that patients with GI and GU cancer may be at higher risk for bleeding complications with a DOAC, the ECOG score and underlying tumour types in each of the four RCTs are presented in Table 6.

Table 6. ECOG score and underlying tumour type in RCTs comparing a DOAC with dalteparin

	Hokusai-VTE cancer (15)	SELECT-D (16)	ADAM-VTE (3)	Caravaggio (4)
ECOG 0	29%	30%	41%	31%
ECOG 1	47%	46%	49%	48%
ECOG 2	24%	24%	10%	21%
Colorectal	15%	25%	16%	20%
Lung	15%	12%	17%	17%
Genitourinary	13%	6%	9%	12%
Breast	12%	10%	9%	13%
Pancreatic/HPB	8%	8%	16%	8%
Gynecologic	11%	10%	10%	10%
Upper GI	5%	9%	4%	5%
Hematologic	11%	9%	9%	7%

ECOG = Eastern Cooperative Oncology Group, HPB = hepatobiliary

The underlying tumour type in the Hokusai-VTE trial is generally similar to those observed in the other RCTs, making it difficult to assume any difference in this area can explain differences in bleeding complication rates between the trials. The ADAM-VTE trial enrolled more patients with a better performance status (41% with ECOG 0 score) and the overall mortality in this trial was lower than that observed in the other trials, supporting the contention that patients in the ADAM-VTE trial had less advanced disease.

A meta-analysis of all four RCTs comparing a DOAC with dalteparin performed a subgroup analysis of the risk of GI and GU bleeding associated with a DOAC versus dalteparin. (21) This study reported a non-significant increase in the risk of major GI bleeding in patients treated with a DOAC (2.6% vs. 1.4%, RR 1.85, 95% CI 0.92–3.71) and

a statistically significant increase in major GU bleeding in patients treated with a DOAC (0.7% vs. 0.1%, RR 4.99, 95% CI 1.08–23.08).

The same investigators conducted a subgroup analysis of the risk of major bleeding in patients with GI cancer (includes colorectal, upper GI, pancreatic and hepatobiliary) using six months data from the Hokusai-VTE and SELECT-D trials and reported a higher risk of a major bleed with a DOAC compared with dalteparin (9.3% vs. 4.0%; RR 2.30, 95% CI 1.08–4.08). (21) In patients with non-GI cancer, the risk of major bleeding was not different between a DOAC and dalteparin. (3.9% vs 3.4%; RR 1.16,95%CI 0.55-2.43).

Due to the apparent better performance status of patients in the ADAM-VTE trial, Giustozzi et al. (20) performed a separate meta-analysis of the Hokusai-VTE, SELECT-D and Caravaggio trials in order to reduce the heterogeneity of their overall meta-analysis. This further analysis reported similar results in favour of a DOAC versus dalteparin for VTE recurrence (RR 0.68, 95% CI 0.51–0.90), no difference in the rates of major bleeding (RR 1.36, 95% CI 0.89–2.06) and a DOAC-associated increase risk of CRNMB (RR1.74, 95% CI 1.17–2.59).

In summary, one of the four RCTs reported a statistically significant increase in major bleeding with rivaroxaban versus dalteparin and another of the four RCTs reported statistically significant increases in CRNMB with rivaroxaban versus dalteparin. Two of the meta-analyses reported an increased relative risk of CRNMB with DOACs versus LMWH. The source of the increased bleeding with DOACs versus LMWH appears to be primarily related to GI and GU bleeding and patients with underlying GI cancer appear to be at a higher risk for a major bleeding complication. There is insufficient evidence to determine if the risk of bleeding with any one DOAC is less than or greater thananother.

3.2.2.4. Outcome: Mortality

There were no significant differences in all-cause mortality reported in any of the RCTs nor in the meta-analyses. Three of the four RCTs (Hokusai-VTE, ADAM-VTE, and Caravaggio) reported on VTE-related mortality, which was infrequent, and nosignificant differences were found between DOACs and LMWHs.

3.2.2.5. Outcome: Quality of life

One RCT included an assessment of the effect of a DOAC vs. an LMWH on quality of life. Although quality of life was not listed as either a primary or secondary outcome of the study, the ADAM-VTE trial, which compared apixaban with dalteparin in 300 patients with cancer-associated VTE, had subjects complete a modified Duke Anticoagulation Satisfaction Scale questionnaire on a monthly basis. (3) In general, apixaban was associated with better outcomes across the 13 measures of the scale,including burden of treatment and overall satisfaction with anticoagulant treatment. Further information on the relative effect of rivaroxaban versus LMWHs on patient

satisfaction are expected with the completion of an ongoing trial whose primary outcome is patient-reported satisfaction. (22)

3.2.2.6. Impact of cancer type and performance status

Carrier et al. (2) concluded that it is not clear if patients with a greater burden of cancer would benefit more from a DOAC or an LMWH.

More recently, the meta-analysis by Giustozzi et al. (20) has provided extensive subgroup analysis related to the impact of cancer type and performance status on the relative risk of VTE recurrence and major bleeding with DOACs versus LMWHs. The results (Table 7) show a relatively consistent effect of DOACs versus LMWHs across all subgroups.

Table 7. Subgroup analysis comparing DOACs with LMWHs

RCT subgroups	N studies, N patients	Recurrent VTE RR (95% CI)	Major bleeding RR (95% CI)
All patients	4 studies, 2,894 patients	0.62 (0.43–0.91)	1.31 (0.83–2.08)
Active cancer	4 studies, 2,841 patients	0.61 (0.44–0.86)	1.40 (0.87–2.27)
Metastatic cancer	2 studies, 1,388 patients	0.78 (0.56–1.10)	1.28 (0.82–2.02)
Solid tumour	2 studies, 2,000 patients	0.68 (0.51–0.91)	1.38 (0.86–2.20)
Hematologic cancer	2 studies, 196 patients	0.81 (0.23–2.83)	0.98 (0.21–4.66)
ECOG ≥ 2	2 studies, 488 patients	0.70 (0.37–1.37)	1.48 (0.63–3.46)

RR = relative risk, CI = confidence interval

3.2.2.7. Summary

The following summarizes the comparative effects of DOACs versus LMWHs on the outcomes of interest in this review:

- **Recurrent VTE:** Two of four RCTs found statistically significant improved rates of VTE recurrent with a DOAC (rivaroxaban and apixaban) compared with dalteparin and the remaining two RCTs had non-statistically significant trends in favour of a DOAC. Meta-analyses of all four RCTs report a lower risk of recurrence of VTE with aDOAC versus dalteparin.
- **Bleeding:** One of the four RCTs reported a statistically significant increase in major bleeding with rivaroxaban versus dalteparin and another of the four RCTs reported statistically significant increases in CRNMB with rivaroxaban versus dalteparin. Two of the meta-analyses reported an increased relative risk of CRNMB with DOACs versus LMWHs. The source of the increased bleeding with DOACs versus LMWHs appears to be primarily related to GI and GU bleeding. Patients with underlying GI cancer appear to be at a higher risk for bleeding from a DOAC.
- **Death:** There is no evidence of differences between DOACs and LMWHs for both overall mortality and VTE-associated mortality.

- **Quality of life:** There is limited evidence comparing the quality of life in patients with cancer-associated VTE treated with either a DOAC or an LMWH. One RCT reported improved patient satisfaction with apixaban compared with dalteparin. As quality of life was not stated to be a primary nor secondary outcome in this trial, there is insufficient evidence that there is difference in quality of life between a DOAC and a LMWH.

3.2.3. Comparison of DOACs with VKAs

3.2.3.1. Summary of studies

There have been no RCTs comparing a DOAC with a VKA in patients with cancer. The best evidence that allows for a comparison of these two drug classes comes from the network meta-analysis performed by Ueyama et al. (18), which used a random-effects model to compare all anticoagulants in cancer-associated VTE. They included a total of 20 studies, the nine RCTs included in the network diagram shown in Appendix 4, and cancer patients subgroup analyses from 11 other unique RCTs. A total of 6,699 patients are included in their analysis. Trials involving a VKA used either warfarin or acenocoumarol.

3.2.3.2. Outcome: VTE recurrence

DOAC use was associated with a significant reduction in recurrent VTE when compared with VKAs (RR 0.55, 95% CI 0.39–0.66).

3.2.3.3. Outcome: Bleeding complications

DOAC use was not associated with any difference in the rate of major bleeding (RR 0.90, 95% CI 0.57–1.44) nor in the rate of CRNMB (RR 1.00, 95% CI 0.74–1.35) when compared with VKAs.

3.2.3.4. Outcome: Mortality

Ueyama et al. did not report on the DOAC class effect on overall mortality relative to VKAs but did report on the comparison between individual DOACs and VKAs. The results are summarized as follows:

- Apixaban (RR 0.94, 95% CI 0.75–1.17)
- Edoxaban (RR 1.08, 95% CI 0.90–1.31)
- Dabigatran (RR 1.06, 95% CI 0.63–1.78)
- Rivaroxaban (RR 0.90, 95% CI 0.70–1.14)

3.2.3.5. Outcome: Quality of life

There is no information comparing the quality of life of patients treated with DOACs versus VKAs in cancer-associated VTE.

3.2.3.6. Summary

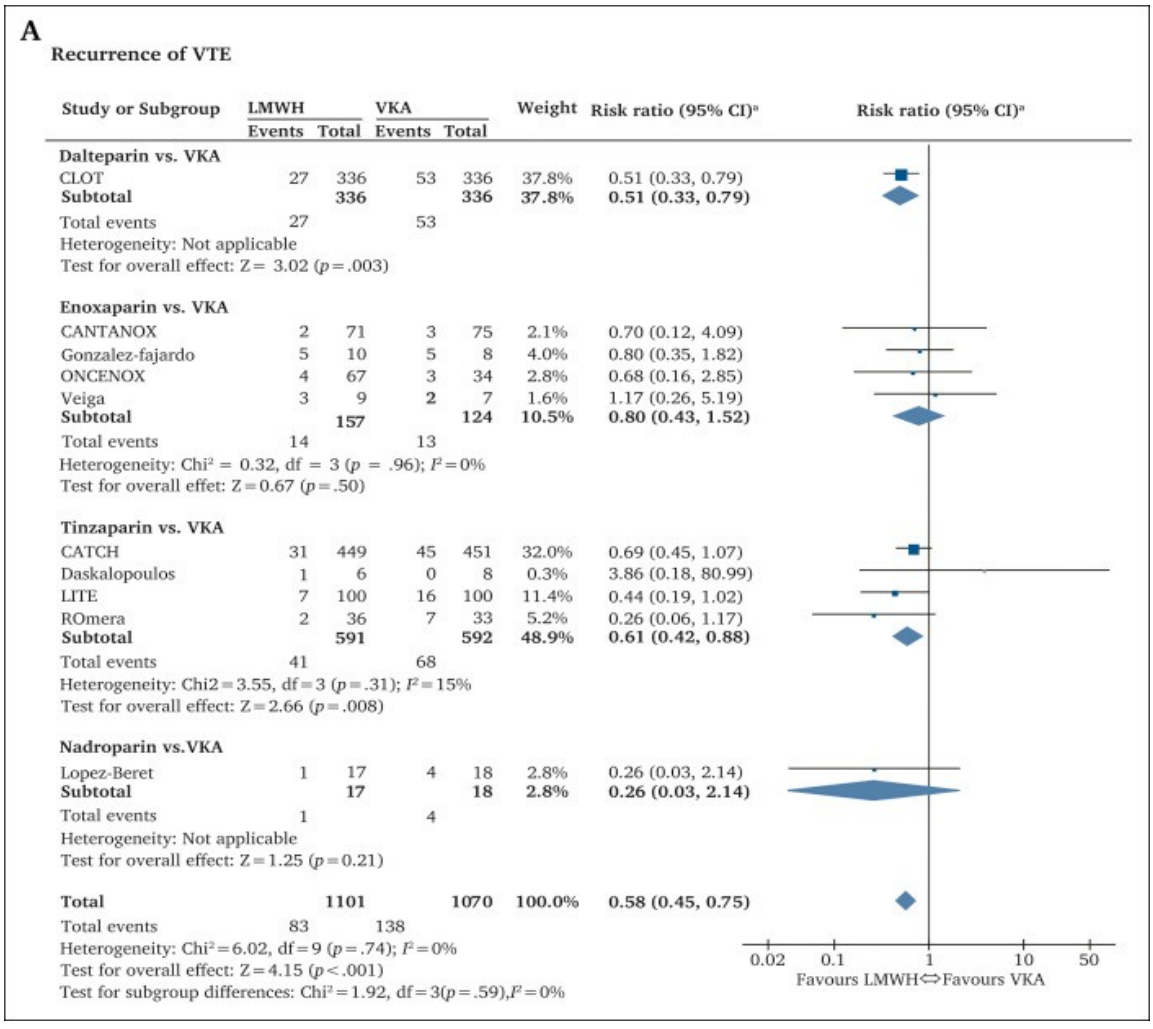
There is no direct evidence comparing DOACs with VKAs in cancer-associated VTE. Indirect evidence from a network meta-analysis supports a reduction in recurrent VTE with DOACs compared with VKAs with no difference in bleeding complicationsor mortality.

3.2.4. Comparison of individual LMWHs

There have been no randomized RCTs comparing individual LMWHs with each other in the treatment of VTE in cancer patients.

While ReVue identified several network meta-analyses comparing LMWHs with either VKAs or DOACs, the majority consider LMWHs as a class. Kirkilesis et al. reported on the effect size of individual LMWHs versus VKAs, and the results are shown in Figure 3. (10)

Figure 3. Recurrence of VTE for individual LMWHs versus VKAs (5)



While ReVue has not identified any studies using a network meta-analysis or indirect comparison to compare individual LMWHs, it is unlikely that either of these approaches would be able to discern any significant differences between the individual LMWHs given the overlap in confidence intervals of the effect of individual LMWHs on VTE recurrence shown in Figure 2.

3.2.5. Comparison of individual DOACs

While there have not been any head-to-head trials comparing individual DOACs, their relative effect sizes have been compared in a network meta-analysis study.

Fuentes et al. (23) reported no significant differences between comparisons ofedoxaban, rivaroxaban, and apixaban on the endpoint of VTE recurrence from a network meta-analysis of the Hokusai-VTE cancer, SELECT-D and ADAM-VTE trials, respectively. (3, 15, 16) The results are summarized as follows:

- Apixaban vs. rivaroxaban: odds ratio 0.24 (95% CI 0.03–2.31)
- Apixaban vs. edoxaban: odds ratio 0.15 (95% CI 0.02–1.27)
- Edoxaban vs. rivaroxaban: odds ratio 1.59 (95% CI 0.61–4.13)

Similarly, no significant differences were found between the individual DOACs with respect to major bleeding:

- Apixaban vs. rivaroxaban: odds ratio 0.1 (95% CI 0.00–2.54)
- Apixaban vs. edoxaban: odds ratio 0.15 (95% CI 0.00–2.40)
- Edoxaban vs. rivaroxaban: odds ratio 0.94 (95% CI 0.30–2.99)

The network meta-analysis by Ueyama et al. (18) included four RCTs of DOACs in cancer-associated VTE (two with apixaban and one each with rivaroxaban and edoxaban) and a further four unique RCTs involving a DOAC (one each with apixaban, dabigatran, edoxaban and rivaroxaban) that reported on a subgroup of cancer patients. Using apixaban as the reference case, the following results were reported on the endpoint of recurrent VTE:

- Edoxaban vs. apixaban: risk ratio 1.20 (95% CI 0.69–2.10)
- Rivaroxaban vs. apixaban: risk ratio 1.12 (95% CI 0.56–2.23)

There were also no statistically significant differences between the individual DOACs with respect to major bleeding.

Given the overlapping confidence intervals from these two network meta-analyses, there is no evidence that one DOAC is superior to another with respect to VTE recurrence.

3.2.6 Conclusion

There have been five RCTs comparing an LMWH with a VKA and four RCTs comparing a DOAC with dalteparin. There have also been a number of meta-analyses and network meta-analyses that have incorporated the results from these trials. Based on the information from these studies, the following conclusions can be drawn.

- There is no evidence from RCTs that VKAs are superior to LMWHs. One of five RCTs reported that an LMWH was superior to warfarin with respect to recurrent VTE, and another RCT reported a lower rate of CRNMB with an LMWH vs. a VKA. Meta-analyses consistently report that LMWHs are superior to VKAs with respect to recurrent VTE, with no difference in the rates of bleeding complications.
- Two of four RCTs comparing a DOAC with dalteparin report that DOACs are associated with a lower rate of VTE recurrence. However, one RCT reported that a DOAC was associated with a higher rate of major bleeding, and another reported a higher rate of CRNMB with a DOAC. Meta-analysis and network meta-analyses support the superiority of DOACs vs. LMWHs on VTE recurrence, with no significant differences in major bleeding complications. Two of the meta-analyses reported an increased relative risk of CRNMB with DOACs versus LMWHs. The source of the increased bleeding with DOACs versus LMWHs appears to be primarily related to GI and GU bleeding. Patients with underlying GI cancer appear to be at a higher risk for bleeding from a DOAC.
- There have been no direct comparisons between a DOAC and a VKAs, although network meta-analyses report that DOACs are superior on VTE recurrence, with no difference in bleeding complications.
- There is insufficient evidence that any antithrombotic drug class differs from another on mortality or quality of life.
- There is no evidence that any one LMWH is superior to another; nor is there any evidence that one DOAC is superior to another. Based on two network meta-analyses, there is no evidence that one DOAC is superior to another with respect to VTE recurrence.

3.3. Research Question 2. A systematic review of LMWHs and DOACs for the secondary prophylaxis (≥ 6 months) of VTE in cancer patients

3.3.1. Summary of studies

The majority RCTs evaluating anticoagulant therapy in cancer-associated VTE had duration of therapy of three to six months. Carrier et al. (2) identified three prospective trials that evaluated therapy beyond six months, the DALTECAN (24), TiCAT (25) and Hokusai-VTE cancer studies. (15) Of note, none of these trials randomized patients to receive an antithrombotic agent after the completion of treatment for an index case of VTE.

The Hokusai-VTE was an RCT comparing edoxaban with dalteparin with a duration of 12 months while DALTECAN and TiCAT were prospective cohort studies, each with a primary objective to evaluate the safety of dalteparin and tinzaparin, respectively, for up

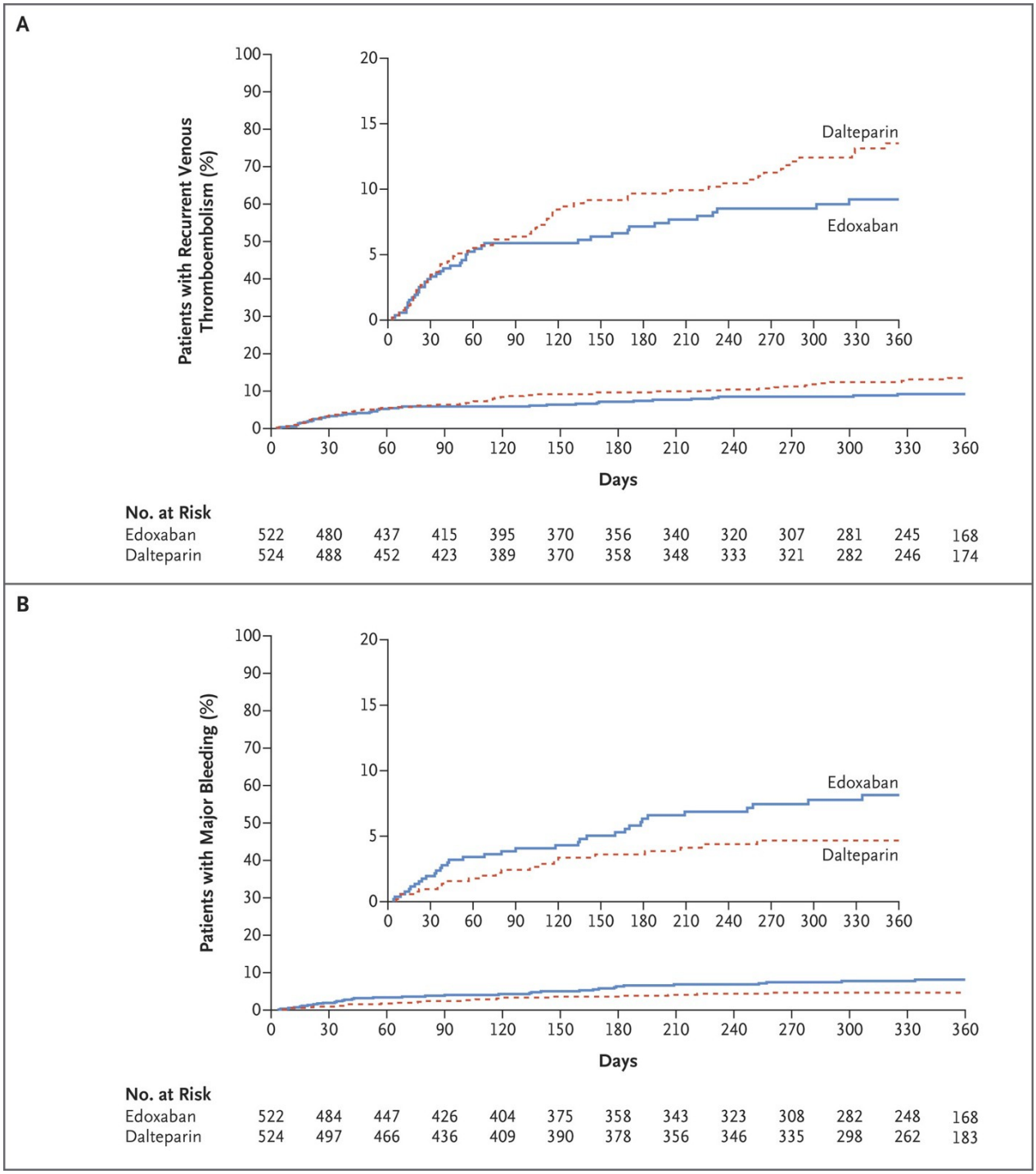
to 12 months of therapy. Carrier et al. concluded that the evidence for secondary prophylaxis was weak and that decisions regarding treatment extension beyond six months should be based on the individual patient's cancer status and treatment as well as risk factors for bleeding. (2)

The DALTECAN study prospectively enrolled 334 patients with active cancer and a newly diagnosed VTE to receive dalteparin for up to 12 months. Withdrawal from the study was common with 185 (55%) completing six months and 109 (32%) completing 12 months. The most common reasons for withdrawal were death (73 subjects, 33.2%), an adverse event (60 subjects, 26.2%) or withdrawal of consent (42 subjects, 18.3%). (24)

The TiCAT study prospectively evaluated 247 patients with active cancer and VTE who were treated with tinzaparin indefinitely. The primary outcome was to compare the incidence of clinically relevant bleeding (major bleeding plus CRNMB) during the first six months of therapy versus months seven to 12. As with the DALTECAN trial, withdrawals rates were high with 198 (80%) and 136 (55%) of patients completing six and 12 months, respectively. (25) Death was the reason for withdrawal in 39 patients at six months and an additional 23 patients between months seven to 12. At 12 months, death accounted for 56% of all withdrawals. Other causes for withdrawal were not reported on.

The Hokusai-VTE cancer study compared 12 months of therapy with either edoxaban or dalteparin in cancer-associated VTE. The key endpoints have been previously summarized in Table 3. (15) Kaplan-Meir event rate curves for recurrent VTE and major bleeding over the 12 months of the study are shown in Figure 4.

Figure 4. Kaplan-Meir event rates over time in the Hokusai-VTE cancer trial



A meta-analysis by Dong et al., which compared DOACs with LMWHs in cancer-associated VTE included two RCTs and nine cohort studies published up to October 2018, performed a subgroup analysis on the relative risk of recurrent VTE and major bleeding at three, six, and 12 months' duration of therapy. (26) The results are summarized in Table 8.

Table 8. Relative risk of recurrent VTE and major bleeding for DOACs vs. LMWHs by duration of treatment (26)

	Recurrent VTE (RR, 95% CI)	Major Bleeding (RR, 95% CI)
3 months of therapy	0.27 (0.07–1.04)	0.94 (0.64–1.39)
6 months of therapy	0.74 (0.60–0.92)	1.23 (0.90–1.69)
12 months of therapy	0.71 (0.59–0.86)	1.47 (0.97–2.23)

3.3.2. Outcome: VTE recurrence

The incidence of recurrent VTE in the DALTECAN study was a secondary endpoint and occurred in 8.7% of subjects during the first six months of therapy and 4.1% during months seven to 12. (24) In the TiCAT study, VTE recurrence was also a secondary endpoint and the percentage of patients with VTE recurrence was 4.5% during the first six months of therapy compared with 1.1% during months seven to 12. (25)

The Hokusai-VTE cancer trial did not report a difference in VTE recurrence rate between edoxaban and dalteparin. While Figure 3 appears to show continued separation of the VTE recurrence event curves for edoxaban and dalteparin from six to 12 months, no conclusions can be drawn due to the lack of a statistically significant difference. (15) Also, there was significant patient withdrawal from the study over this time period in both groups: 38.3% of edoxaban patients completed 12 months of treatment or until study closure versus 29.4% of dalteparin patients. The leading reasons for withdrawal inthe edoxaban arm were death (16.5%), a clinical outcome or adverse event (15.1%) and cancer progression (10.2%). The leading reasons for withdrawal in the dalteparin arm were death (19.1%), patient decision re: inconvenience of dosing (14.9%) and a clinical outcome or adverse event (11.8%).

Results from the meta-analysis by Dong et al. (26) reported relatively consistent differences in the rate of VTE recurrence between a DOAC and an LMWH for the subgroups of three, six, and 12 months of therapy.

3.3.3. Outcome: Bleeding complications

The primary outcome of the DALTECAN study was major bleeding at months seven to 12 and this occurred in 0.7% of subjects compared with an incidence of major bleeding of 1.7% within the first six months of therapy. (24) The primary outcome of the TiCAT study was a composite of major bleeding and CRNMB and this occurred at a rate of0.9% patient-month during the first six months versus 0.6% patient-month during months seven to 12. (25)

The Hokusai-VTE trial reported a higher rate of bleeding with edoxaban compared with dalteparin and the Kaplan-Meir curve appears to show continued separation of major bleeding events through to one year. (15) However, no conclusions can be made given the high number of patient withdrawals over this period.

The meta-analysis by Dong et al. (26) reported no differences in the rates of major bleeding between DOACs and LMWHs for the subgroups of three, six, and 12 months of therapy.

3.3.4 Conclusion

A placebo-controlled trial of an antithrombotic agent in patients who had previously completed a treatment course for cancer-associated VTE would be helpful in clarifying the effectiveness and safety of such therapy. However, there have been no placebo-controlled trials in patients with cancer-associated VTE who have completed an initial six-month course of antithrombotic therapy. Limited evidence from prospective studies of 12 months' duration suggests that the risk of bleeding complications with DOACs and LMWHs are relatively lower during months six to 12 when compared with the first six months of therapy but there is insufficient information regarding their effectiveness. Therefore, evidence for extending anticoagulation beyond six months in patients with cancer-associated VTE is very limited.

SECTION D – COST-EFFECTIVENESS REVIEW

1. Objective

To identify, analyze and synthesize published information on the relative cost-effectiveness of antithrombotic agents and classes in cancer-associated VTE. As this information will inform public drug funding decisions in the Canadian context, literature from Canada or jurisdictions with similar public-funded drug programs are prioritized.

2. Literature Search Strategy

The initial focus of this work was on the clinical effectiveness of VKAs, LMWHs, and DOACs in cancer-associated VTE. The literature search strategy for this identified some publications dealing with cost-effectiveness and on further discussion it was agreed to conduct a more in-depth literature search for cost-effectiveness of antithrombotics in VTE. This search strategy, which was run on July 6, 2020, is shown in Appendix 5. Databases included in the search were Ovid Medline, Embase and the grey literature (Grey Matters/Internet). ReVue specifically screened for publications from the following jurisdictions: Canada, Australia, European Union, New Zealand and the United Kingdom.

The abstracts of articles identified were independently reviewed by two individuals to determine if they met the eligibility criteria. Any disagreement on the initial review was resolved by discussion until a consensus was reached. The full text of studies meeting the eligibility criteria was retrieved for further review.

3. Literature Search Results

The clinical literature search strategy (see Section A) identified three citations of potentially relevant cost-effectiveness studies:

- Dranitsaris G, et al. Low-molecular-weight heparins for the prevention of recurrent venous thromboembolism in patients with cancer: A systematic literature review of efficacy and cost-effectiveness. J Oncol Pharm Practice 2019;25:68–75.
- Dranitsaris G, et al. Dalteparin versus vitamin K antagonists for the prevention of recurrent venous thromboembolism in patients with cancer and renal impairment: a Canadian pharmacoeconomic analysis. Clin Econ and Outcomes Res 2017;9:65-73.
- Streiff M, et al. Healthcare resource utilization and costs associated with venous thromboembolism in cancer patients treated with anticoagulants. J Med Econ 2019;22:1134-40.

The search strategy outlined in Appendix 5 identified 40 publications of interest. Two reviewers independently reviewed these and excluded 36 for the following reasons:

- Eight excluded, as they were published in abstract form only;
- Six excluded, as they dealt with post-operative prophylaxis only;
- Six excluded, as they were done from a US perspective;
- Five excluded, as they did not deal with antithrombotic drugs;
- Four excluded, as they were not in a cancer population;
- Four excluded, as they were not cost-effectiveness studies;
- Three excluded, as they dealt with primary prophylaxis only.

Of the remaining four publications, two were duplicates of studies found in the initial clinical search strategy (Dranitsaris 2019, Streiff 2019), which resulted in five unique publications for further review.

4. Analysis of Literature

The findings and strengths and weaknesses of the selected publications are reviewed below.

The Ontario Drug Policy Review Network (ODPRN) published a pharmacoeconomic review of LMWHs in the treatment and secondary prevention of VTE in patients with cancer in April 2016. (27) Given the lack of published economic evaluations that met the requirements for a robust evaluation, a de novo economic evaluation was performed from an Ontario perspective and using data from the CLOT study, which was published in 2003 (6) and which found that dalteparin reduced the recurrence of VTE from 17% to 9% when compared with warfarin. The incremental cost-effectiveness ratio (ICER) for an LMWH versus warfarin exceeded $1M per quality-adjusted life year (QALY), and it was determined that a price reduction of > 85% for LMWHs would be required to achieve a $50,000 per QALY threshold. The strengths of this paper include its independence, Canadianperspective and the de novo economic modelling, but its usefulness for this review islimited by the lack of inclusion of DOACs as comparators.

Dranitsaris et al. published an economic evaluation of dalteparin versus warfarin in cancer patients with renal impairment. (28) They also used data from the CLOT trial but focused on a post hoc subgroup analysis of patients with moderate to severe renal impairment who had VTE recurrence reduced from 17% on warfarin to 3% on dalteparin. The reported cost-utility with dalteparin versus warfarin in this study was CAD$23,100 in the overall CLOT study population and $14,000 in the subgroup of patients with renal failure. The most notable factor influencing the vastly different results reported above by the ODPRN group is that Dranitsaris et al. reported a QALY gain of 0.28 with dalteparin versus warfarin while this value was 0.002 in the ODPRN group. This 140-fold difference is likely due to the different ways the two groups used to estimate the quality of life in this population. While both groups used a time trade-off methodology, the ODPRN group based their utilities onpublished literature from relevant patient groups (those with cancer and those with VTE)

while Dranitsaris et al. used information from interviews with 24 randomly selected members of "the tax-paying general public." As with the ODPRN report, Dranitsaris et al. did not include DOACs in their analysis. Also, there is a risk of bias in the Dranitsaris study in that it was sponsored by Pfizer Inc. (manufacturer of dalteparin), and three of the study authors were employees of Pfizer.

The 2019 study by Dranitsaris et al. (29) included a systematic review of RCTs comparing four LMWHs (dalteparin, enoxaparin, nadroparin, tinzaparin) with VKAs in cancer-associated VTE and a literature review of published economic studies of LMWHs that would allow comparison of one LMWH with another. They reported that of the six RCTs included in the analysis, only two were of high quality and adequately powered (one each with dalteparin and tinzaparin) and that only the study with dalteparin reported a statistically significant benefit over warfarin with respect to VTE recurrence. They also cited four studies evaluating the cost-effectiveness of dalteparin, all four of which were published by the Dranitsaris group and all were sponsored by Pfizer. These studies reported that dalteparin was a cost-effective alternative when compared with warfarin (Canadian ICERs of $13,800–$41,200 per QALY). Again, there is a risk of bias in this study in that two of the three study authors were employees of Pfizer and funding of the study was provided by Pfizer.

A review of the paper by Streiff et al. (30) revealed that it was a cost-benefit analysis of patients treated with warfarin, LMWHs or rivaroxaban from a US claims database (Humana). As such, it was not felt to be relevant to Canadian jurisdictions.

The most comprehensive economic evaluation of anticoagulants in cancer-associated VTE was published by the National Institute for Health and Care Excellence (NICE) in March 2020. (31) This economic evaluation was part of a larger report on the management of venous thromboembolic disease. The information below focuses solely on the use of anticoagulants in cancer-associated VTE.

Due to a lack of reliable published economic evaluations, NICE developed a de novo economic model. The model was developed for adults with a confirmed VTE and a subgroup analysis was performed in people with cancer. The model assumed a six-month duration of treatment and used a cost-utility analysis from a National Health Service perspective with a lifetime horizon and a discount rate of 3.5% per year. The methodology used by NICE included a network meta-analysis of 11 active-comparator RCTs of anticoagulants in cancer-associated VTE, which included all of the RCTs included in the clinical evidence review with the exception of the two studies of apixaban versus dalteparin published in early 2020. (3, 4) At the direction of the NICE Committee, VKAs and LMWHs were each considered as a class, while DOACs were considered individually.

Separate results were produced for patients with deep vein thrombosis (DVT) and for those with pulmonary embolus (PE) and the results are shown in Tables 9 and 10 below.

Table 9. Incremental cost-effectiveness in cancer patients with DVT

Intervention	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
Edoxaban	£19,538	1.39			
LMWH/VKA	£19,650	1.412	£112	0.022	£5,080
Rivaroxaban	£19,697	1.418	£47	0.006	£7,716
UFH/VKA	£19,713	1.407	£16	−0.011	Dominated
Apixaban	£19,794	1.426	£97	0.008	£12,728
Dabigatran	£19,803	1.396	£9	−0.030	Dominated
LMWH	£21,287	1.418	£1,494	−0.008	Dominated

QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio, UFH = unfractionated heparin

Table 10. Incremental cost-effectiveness in cancer patients with PE

Intervention	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
Edoxaban	£19,363	1.368			
LMWH/VKA	£19,440	1.386	£78	0.018	£4,340
UFH/VKA	£19,493	1.379	£52	−0.007	Dominated
Rivaroxaban	£19,521	1.397	£81	0.010	£7,826
Dabigatran	£19,598	1.371	£77	−0.025	Dominated
Apixaban	£19,599	1.402	£78	0.005	£15,378
LMWH	£21,094	1.395	£1,496	−0.007	Dominated

QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio, UFH = unfractionated heparin

Due to uncertainty in the level of clinical evidence, a probabilistic sensitivity analysis was performed, and it showed that, in cancer patients with DVT when one QALY is valued at £20,000, apixaban had a 49% probability of being the preferred choice, while rivaroxaban and unfractionated heparin/VKA have probabilities of 23% and 16% of being preferred, respectively. For patients with a PE, apixaban had a 51% probability of being the preferred treatment option, while rivaroxaban and unfractionated heparin/VKA have probabilities of 26% and 13%, respectively. For both DVT and PE, therapy solely using a LMWH had a 0% chance of being cost- effective, due to its higher acquisition cost.

Based on these results and after deliberation on a variety of other considerations, the NICE Committee provided the following recommendations.

- That a DOAC be considered for the treatment of cancer-associated VTE.
- That they could not recommend one DOAC over another.
- That if a DOAC is deemed to be unsuitable, an LMWH alone or an LMWH followed by warfarin should be considered.
- That due to uncertainty regarding the clinical inputs into the economic model, that the recommendations may need to be updated based on the results of the ADAM-VTE and Caravaggio studies. (3, 4)

5. Discussion

With the exception of the report by NICE, published reports on the cost-effectiveness of anticoagulants in cancer-associated suffer from a number of limitations including lack of inclusion of DOACs, a significant risk of bias and a lack of relevance to a publicly funded drug system.

The NICE report addresses all of these limitations and additionally has the strengths of using an independent network meta-analysis and a de novo economic model. The NICE Committee recommended that a DOAC is the preferred choice for anticoagulation in cancer-associated VTE but that the results of two recently published RCTs comparing apixaban with dalteparin should be considered.

As outlined in the clinical report, the ADAM-VTE trial reported that apixaban resulted in a significant reduction in VTE recurrence and no difference in the risk of major bleeding when compared with dalteparin. (3) The Caravaggio trial reported no statistically significant differences in VTE recurrence or major bleeding with apixaban versus dalteparin, though there was a non-statistically lower rate of VTE recurrence with apixaban (Hazard ratio 0.63, 95% confidence interval 0.37–1.07). (4) Taken together, it is likely that if these results were incorporated into the NICE model it would result in increased confidence in the cost-effectiveness of DOACs over LMWHs.

6. Conclusion

Despite a relative lack of robust economic evaluations and uncertainty regarding clinical effectiveness and safety inputs, it appears that a DOAC is a cost-effective option for the treatment of cancer-associated VTE. At current drug acquisition costs, it is unlikely that LMWHs are a cost-effective option.

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31. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Evidence reviews for pharmacological treatment in people with suspected or confirmed deep vein thrombosis and/or pulmonary embolism [NICE guideline NG158]. 2020 Mar. NICE. https://www.nice.org.uk/guidance/ng158/evidence/d-pharmacological-treatment-pdf-8710588337

Appendix 1. Canadian Public Drug Plan Coverage of LMWHs and DOACs in Cancer-Associated VTE

The following chart provides a summary of antithrombotic coverage policies across Canada. There are some patterns that are apparent from the comparison chart, including:

Low molecular weight heparins (LMWHs)

- Some provinces and territories have moved LMWHs to unrestricted status (Alberta, Quebec, Nova Scotia, Northwest Territories, Nunavut).
- Those regions with restrictions in place permit use for different durations. In general, the duration of use is intended to be short-term therapy (10–30 days) for VTE to bridge patients onto another therapy (e.g., warfarin, heparin) or permit six months of therapy for patients should not be receiving warfarin due to contraindications, treatment failure and/or inability to safely monitor the response to warfarin (international normalized ratio; INR).
- Some regions restrict choice of LMWHs by indication, whereas others are more flexible. For example, for use after cancer-associated VTE, British Columbia permits dalteparin and tinzaparin, whereas New Brunswick permits any of the four LMWHs to be used.

Direct oral anticoagulants (DOACs)

- The majority of regions restrict DOACs (all but Saskatchewan). Saskatchewan's policy of not restricting DOACs may be influenced by the lower daily cost of DOACs relative to LMWHs.
- The majority of regions that restrict DOACs place a six-month limit on the duration, indicating that after six months warfarin/heparin become more cost-effective. There is some language coaching prescribers that if they intend to treat the patient for more than six months, they should begin with warfarin/heparin.

Province/ Territory	**LMWHs** (DAL = dalteparin, EN = enoxaparin, N = nadroparin, T = tinzaparin)	**DOACs** (A = apixaban, DAB = dabigatran, ED = edoxaban, R = rivaroxaban)	**Comments**
British Columbia	Restricted – 6 months for patients, associated with cancer, who have failed, or who are unable to tolerate, oral therapy with warfarin. (DAL, T)	Restricted – 6 months for treatment of VTE	Practitioner completes generic request form, which includes options to indicate contraindications and previously tried therapies. Some variability in listing between LMWHs. DOACs stated to be not cost-effective vs. heparin/warfarin after 6 months. Edoxaban not listed. Dabigatran is listed only for A-fib indication.
Alberta	Unrestricted	Restricted – 6 months for VTE when heparin/warfarin contraindicated or patient unable to monitor INR (A, ED, R)	Practitioner completes DOAC-specific request form indicating contraindication or inability to monitor INR.
Saskatchewan	Restricted – 10 days for VTE (DAL, EN, N, T) – Long-term for prophylaxis for patients with contraindication to, intolerant of, failed warfarin (DAL, EN, N, T)	Unrestricted	Practitioner writes or calls, supplying diagnosis/EDS criteria met. Listing strategy promotes DOACs over long-term LMWHs.
Manitoba	Restricted: criteria and duration not publicly posted. "*Please contact the EDS Program at Manitoba Health for specific criteria.*"	Restricted – 6 months for treatment and prevention of recurrent VTE (A, E, R)	Practitioner completes generic request form, which includes options to indicate contraindications and previously tried therapies.
Ontario	Restricted – 21 days duration for acute DVT (DAL, N) – 21 days duration for acute VTE (EN, T) – Unspecified duration for warfarin contraindication, or failure (presumably intended as prophylaxis; DAL, EN, N, T)	Restricted – 6 months for treatment of VTE (A, ED, R)	Practitioner supplies code on prescription, no application process. Some variability in listing between LMWHs. DOACs stated to be not cost-effective vs. heparin/warfarin after 6 months.

Province/ Territory	**LMWHs** (DAL = dalteparin, EN = enoxaparin, N = nadroparin, T = tinzaparin)	**DOACs** (A = apixaban, DAB = dabigatran, ED = edoxaban, R = rivaroxaban)	**Comments**
Quebec	Unrestricted	Restricted – 6 months for VTE treatment (A, R) – 12 months for VTE treatment (ED) – 12 months, renewable, for prevention of VTE if physician considers benefits to outweigh risks (A)	
New Brunswick	Restricted – 30 days for VTE (DAL, EN, N, T) – Extended treatment of recurrent VTE while on warfarin (DAL, EN, N, T) – 6 months for treatment and secondary prevention of VTE in cancer patients in whom warfarin is not an option (DAL, EN, N, T)	Restricted – 6 months for treatment of VTE (A, E, R)	Practitioner must submit requests for quantities exceeding 35 days of therapy. DOACs stated to be not cost-effective vs. heparin/warfarin after 6 months
Nova Scotia	Unrestricted	Restricted – 6 months for treatment of VTE (A, ED, R)	Practitioner completes DOAC-specific request form.
Prince Edward Island	Restricted – 30 days for VTE (DAL, EN, T) – Extended treatment of recurrent VTE that has occurred while patients are on therapeutic doses of warfarin (DAL, EN, T) – 6 months for treatment and secondary prevention of VTE in patients with cancer (DAL, EN, T)	Restricted – 6 months for treatment of VTE (A, ED, R)	Practitioner completes LMWH-specific or DOAC-specific request form.

Province/ Territory	**LMWHs** (DAL = dalteparin, EN = enoxaparin, N = nadroparin, T = tinzaparin)	**DOACs** (A = apixaban, DAB = dabigatran, ED = edoxaban, R = rivaroxaban)	**Comments**
Newfoundland and Labrador	Restricted – 10 days for VTE (DAL, EN, T) – 3 months for treatment of recurrent VTE that has occurred while patients are on therapeutic doses of warfarin (DAL, EN, T) – 6 months for the secondary prevention of symptomatic VTE for cancer patients with drug interactions or have failed oral anticoagulation (DAL) – 3 months for prophylaxis of VTE in patients failing to reach therapeutic INR while on oral anticoagulation (DAL, EN, T)	Restricted – 6 months for treatment of VTE (A, ED, R)	Practitioner completes LMWH-specific or DOAC-specific request form.
Yukon	Restricted – Treatment duration not specified – For treatment of approved chronic condition (DAL, EN, N, T) – Long-term outpatient prophylaxis in patients who are intolerant to, or have failed, warfarin therapy (DAL, EN, N, T)	Restricted – 6 months for treatment of VTE (A)	Nuances in drug coverage.
Northwest Territories/ Nunavut	Unrestricted	Restricted – Unspecified duration for treatment of VTE (A, ED, R)	Referencing Non-Insured Health Benefits for First Nations and Inuit.

Appendix 2. Literature Search Strategy

PubMed search strategy (as per Key, et al.)

"Deep-Venous Thrombosis"[tiab] OR "Deep-Venous Thromboses"[tiab] OR "Thrombosis, Deep- Venous" OR "Deep Venous Thrombosis"[tiab] OR "Deep Venous Thromboses"[tiab] OR "Thrombosis, Deep Venous"[tiab] OR "Venous Thrombosis, Deep"[tiab] OR "Deep-Vein Thrombosis"[tiab] OR "Deep-Vein Thromboses"[tiab] OR "Pulmonary Embolism"[Mesh] OR "Pulmonary Embolism"[tiab] OR "Pulmonary Embolisms"[tiab] OR "Pulmonary Emboli"[tiab] OR "Pulmonary Thromboembolisms"[tiab] OR "Pulmonary Thromboemboli"[tiab] OR "Pulmonary Thromboembolism"[tiab])
AND
("antiplatelet therapy"[tiab] OR "Aspirin"[Majr] OR "Aspirin"[tiab] OR "Anticoagulants"[Mesh] OR "Heparin"[Mesh] OR "Heparin"[tiab] OR "Heparin, Low-Molecular-Weight"[Mesh] OR "low molecular weight heparin" OR "Dalteparin"[Mesh] OR "dalteparin"[tiab] OR "Fragmin"[tiab] OR "Enoxaparin"[Mesh] OR "enoxaparin"[tiab] OR "Lovenox"[tiab] OR "tinzaparin"[tiab] OR "Innohep"[tiab] OR "fondaparinux"[tiab] OR "Arixtra"[tiab] OR "Vitamin K antagonist"[tiab] OR "Warfarin"[Mesh] OR "warfarin"[tiab] OR "Coumadin"[tiab] OR "dabigatran"[tiab] OR dabigatran[Mesh] OR "Pradaxa"[tiab] OR "apixaban"[tiab] OR "Eliquis"[tiab] OR "rivaroxaban"[tiab] OR "Xarelto"[tiab] OR "edoxaban"[tiab])
AND
cancer[sb]
AND
English[la]
AND
"Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Meta-Analysis" [Publication Type] OR "Practice Guideline" [Publication Type] OR systematic[sb] OR randomly[tiab] OR randomized[tiab] OR meta-analysis[tiab] OR trial[ti]
AND
search range Jan 2018 through Mar 2020.

PubMed search strategy (as per Carrier, et al.)

("Neoplasms"[Mesh] OR "Carcinoma"[Mesh]) AND ("Venous Thromboembolism"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Venous Thrombosis"[Mesh]) AND ("Anticoagulants"[Mesh] OR "Heparin, Low-Molecular-Weight"[Mesh] OR "Warfarin"[Mesh] OR "apixaban"[Supplementary Concept] OR "Dabigatran"[Mesh] OR "edoxaban"[Supplementary Concept] OR "Rivaroxaban"[Mesh])
Search range Jan 2017 through March 2020.

PubMed search strategy (as per Farge, et al.)

Cancer AND Venous Thromboembolism AND Anticoagulant Drugs and Devices
Search range Jan 2018 through Mar 2020

EMBASE (search string developed by ReVue)

exp venous thromboembolism/
exp vein thrombosis/
exp upper extremity deep vein thrombosis/
exp deep vein thrombosis/
exp lung embolism/
(thrombosis or thromboses or embolism or embolisms or emboli or thromboembolism or thromboembolisms or thromboemboli).m_titl.

(thrombosis or thromboses or embolism or embolisms or emboli or thromboembolism or thromboembolisms or thromboemboli).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
1 or 2 or 3 or 4 or 5 or 6 or 7
exp antithrombocytic agent/
exp acetylsalicylic acid/
exp anticoagulant agent/
exp heparin/
exp low molecular weight heparin/
exp fondaparinux/
exp antivitamin K/
exp warfarin/
exp apixaban/
exp rivaroxaban/
exp edoxaban/
exp dabigatran/
exp dabigatran etexilate/
exp dalteparin/
exp enoxaparin/
exp tinzaparin/
roparin/
(antiplatelet or anticoagulant or heparin or dalteparin or enoxaparin or tinzaparin or nadroparin or fondaparinux or warfarin or apixaban or rivaroxaban or dabigatran or edoxaban or xarelto or eliquis or pradaxa or pradax or arixtra or fragmin or fraxiparine or lovenox or innohep or lixiana or savaysa).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
(antiplatelet or anticoagulant or heparin or dalteparin or enoxaparin or tinzaparin or nadroparin or fondaparinux or warfarin or apixaban or rivaroxaban or dabigatran or edoxaban or xarelto or eliquis or pradaxa or pradax or arixtra or fragmin or fraxiparine or lovenox or innohep or lixiana or savaysa).m_titl.
9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
neoplasm/
(neoplasm or cancer).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
(neoplasm or cancer).m_titl.
29 or 30 or 31
clinical study/
exp meta analysis/
exp “systematic review”/
(clinical trial or random or randomized or “meta-analysis” or systematic).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
(clinical trial or random or randomized or “meta-analysis” or systematic).m_titl.
33 or 34 or 35 or 36 or 37
8 and 28 and 32 and 38
limit 39 to (human and english language and yr = “2018-Current”)

Cochrane (search string developed by ReVue)

MeSH descriptor: [Neoplasms] explode all trees
MeSH descriptor: [Carcinoma] explode all trees
(#1 or #2)
(“deep vein thromboses”):ti,ab,kw OR (“deep vein thrombosis”):ti,ab,kw OR (“deep-vein thromboses”):ti,ab,kw OR (“deep-vein thrombosis”):ti,ab,kw OR (“deep venous thrombosis”):ti,ab,kw

("pulmonary emboli"):ti,ab,kw OR ("pulmonary embolism"):ti,ab,kw OR ("pulmonary embolus"):ti,ab,kw OR ("pulmonary thrombo-embolism"):ti,ab,kw OR ("pulmonary thrombo-embolisms"):ti,ab,kw
("pulmonary thrombo-embolic disease"):ti,ab,kw OR ("pulmonary thrombo-embolic diseases"):ti,ab,kw OR ("pulmonary thromboembolic disease"):ti,ab,kw OR ("pulmonary thrombo-embolic disease"):ti,ab,kw
MeSH descriptor: [Embolism and Thrombosis] explode all trees
#4 or #5 or #6 or #7
MeSH descriptor: [Anticoagulants] explode all trees
("acetylsalicylic acid"):ti,ab,kw OR ("unfractionated heparin"):ti,ab,kw OR ("low molecular weight heparin"):ti,ab,kw OR ("fondaparinux"):ti,ab,kw OR ("Warfarin"):ti,ab,kw
("dalteparin"):ti,ab,kw OR ("enoxaparin"):ti,ab,kw OR ("nadroparin"):ti,ab,kw OR ("tinzaparin"):ti,ab,kw
("rivaroxaban"):ti,ab,kw OR (edoxaban):ti,ab,kw OR (apixaban):ti,ab,kw OR (dabigatran):ti,ab,kw
#9 or #10 or #11 or #12
MeSH descriptor: [Clinical Trial] explode all trees
MeSH descriptor: [Comparative Study] explode all trees
MeSH descriptor: [Meta-Analysis] explode all trees
MeSH descriptor: [Multicenter Study] explode all trees
MeSH descriptor: [Systematic Review] explode all trees
("clinical trial"):ti,ab,kw OR ("randomized"):ti,ab,kw
#14 or #15 or #16 or #17 or #18 or #19
#3 and #8 and #13 and #20
#21 with Cochrane Library publication date Between Jan 2018 and Apr 2020, in Cochrane Reviews, Trials (Word variations have been searched)

Appendix 3. Summary of Clinical Practice Guidelines of Antithrombotics in Cancer-Associated VTE

Guideline	Treatment 1st line	Treatment 2nd line	Secondary prevention 1st line	Secondary prevention 2nd line	Comments
Kearon C, et al. CHEST 2016 CHEST guideline and expert panel report	LMWH	One of: – VKA – Dabigatran – Rivaroxaban – Apixaban – Edoxaban	**Long-term/secondary prevention** No recommendation on drug of choice for secondary prevention. LMWH, DOACs, or VKAs should be offered to select patients with active cancer, reassessed intermittently. Duration of treatment beyond 3 months dependent on whether VTE was provoked, and whether the risk is transient.		
Farge D, et al. Lancet Oncol 2019 International Society on Thrombosis and Haemostasis	**Initial treatment** LMWH if creatinine clearance 30 mL/min ormore **Early maintenance (up to 6 months)** – LMWH	**Initial treatment** – UFH – Rivaroxaban in the first 10 days – Edoxaban, overlapping with a parenteral agent – Fondaparinux **Early maintenance (up to 6 months)** – VKAs – DOACs if creatinine clearance 30 mL/min or more, without strong drug-drug interactions, without absorption impairment, and without gastrointestinal tract malignancies – some agent-specific context	**Long-term/secondary prevention** No recommendation on drug of choice for secondary prevention. LMWHs, DOACs, or VKAs should be offered to select patients withactive cancer, reassessed intermittently. After 6 months reassess benefits and risks of continuing therapy.		Selection of treatment option is influenced by patient risk factors, values and preferences. Accordingly, the guideline does not explicitly state which agents are first and second line options.

Guideline	Treatment 1st line	Treatment 2nd line	Secondary prevention 1st line	Secondary prevention 2nd line	Comments
Key NS, et al. J Clin Oncol 2019	**Initial 5–10 days** LMWH, UFH, fondaparinux, rivaroxaban. If parenteral, LMWH preferred over UFH. R*ecommendation 4.1* **10 days to 6 months** LMWHs, edoxaban, or rivaroxaban for at least 6 months are preferred *Recommendation 4.2*	**Initial 5–10 days** If parenteral, UFH is the second line option. Unclear whether fondaparinux is viewed similarly to LMWH or as to UFH R*ecommendation 4.1* **10 days to 6 months** Vitamin K antagonists are inferior but may be used if LMWHs or direct oral anticoagulants (DOACs) are not accessible. *Recommendation 4.2*	**Beyond 6 months** No recommendation on drug of choice for secondary prevention. LMWHs, DOACs, or VKAs should be offered to select patients withactive cancer, reassessed intermittently. *Recommendation 4.3*		
NICE guideline NG158 2020March26 – **no renal impairment, active cancer or antiphospholipid syndrome**	One of: – Apixaban – Rivaroxaban	One of: – LMWH then dabigatran or edoxaban – LMWH and VKA for 5 days or stable therapeutic INR, then VKA alone	No recommendations on drug of choice for secondary prevention, after an initial 3–6 months of treatment. After 3 months (3–6 months for active cancer) reassess benefits and risks of continuing therapy.		
NICE guideline NG158 2020March26 – **renal impairment**	15–50 mL/min, one of – apixaban – rivaroxaban – LMWH then dabigatran or edoxaban – LMWH and VKA for5 days or stable therapeutic INR, then VKA alone	Not identified	No recommendations on drug of choice for secondary prevention, after an initial 3–6 months of treatment. After 3 months (3–6 months for active cancer) reassess benefits and risks of continuing therapy.		

Guideline	Treatment 1st line	Treatment 2nd line	Secondary prevention 1st line	Secondary prevention 2nd line	Comments
NICE guideline NG158 2020March26 **severe renal impairment**	Below 15 mL/min, one of – LMWH – UFH – LMWH and VKA for5 days or stable therapeutic INR, then VKA alone	Not identified	No recommendations on drug of choice for secondary prevention, after an initial 3–6 months of treatment. After 3 months (3–6 months for active cancer) reassess benefits and risks of continuing therapy.		
NICE guideline NG158 2020March 26 **active cancer**	DOAC	One of: – LMWH – LMWH and VKA for 5 days or stable therapeutic INR, then VKA alone	No recommendations on drug of choice for secondary prevention, after an initial 3–6 months of treatment. After 3 months (3–6 months for active cancer) reassess benefits and risks of continuing therapy.		
Streiff MB, et al. NCCN clinical practice guidelinesin oncology, 2020Apr16, Version 1.2020 https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf	Patients without gastric or gastroesophageal lesions – Apixaban – LMWH or UFH then edoxaban – Rivaroxaban Patients with gastric or gastroesophageal lesions – Dalteparin – Enoxaparin	One of: – LMWH, dalteparin or enoxaparin – Dabigatran – Fondaparinux – UFH – Warfarin and one of LMWH, fondaparinux, UFH	No recommendations on drug of choice for secondary prevention, after an initial 3 monthsof treatment. After 3 months, assess whether cancer or cancer therapy are still active, and reassess benefits and risks of continuing therapy.		Guidelines for selection of agent is based on a list of considerations, including renal and hepatic function, ease of use, monitoring, bleeding risk, ease of reversal of effect, cost, inpatient or outpatient status. Agents are not labelled strictly as first or second line.
Carrier M, et al. Curr Oncol 2018	Text in publication states that LMWHs are superior to VKAs, and that DOACs are non-inferior to LMWHs, with edoxaban having the strongest evidence base. The treatment algorithm encourages risk stratification by bleeding risk (LMWHs preferred for higher risk), high-risk cancers (LMWHs preferred for higher risk) and drug interactions (LMWHs where pharmacokinetic drug interactions a concern with DOACs).		No recommendations on drug of choice for secondary prevention, after an initial 6 monthsof treatment. Implied in the document and algorithm, is that patients would stay on the agent used to treatthe embolism.		Treatment algorithm is constructed to select agents based on risk stratification of patients, rather than explicitly identifying first and second line options.

Appendix 4. Included Studies

#	Primary author	Title	Citation
1	Alikhan R	Cancer associated thrombosis and direct oral anticoagulants:A meta-analysis of randomised clinical trials.	Research and Practice in Thrombosis and Haemostasis. Conference: 27th Congress of the International Society on Thrombosisand Haemostasis. Australia. 3 (Supplement 1) (pp 727-728), 2019. Date of Publication: July 2019.
2	Barbarawi M	The role of anticoagulation in venous thromboembolism primary prophylaxis in patients with malignancy: A systematic review and meta-analysis of randomized controlled trials.	Thromb Res. 2019 Sep;181:36-45. doi: 10.1016/j.thromres.2019.07.007.Epub 2019 Jul 16.
3	Brunetti ND	Direct oral anticoagulants more effective than low-molecular-weight heparin for venous thrombo-embolism in cancer: an updated meta-analysis of randomized trials.	Journal of Thrombosis and Thrombolysis. (no pagination), 2019. Date of Publication: 2019.
4	Carrier M	Treatment algorithm in cancer-associated thrombosis: Canadian expertconsensus.	Curr Oncol. 2018 Oct;25(5):329-337. doi: 10.3747/co.25.4266. Epub 2018 Oct 31.
5	Chen H	Prevention of venous thromboembolism in patients with cancer with direct oral anticoagulants: A systematic review and meta-analysis.	Medicine (Baltimore). 2020 Jan;99(5):e19000. doi: 10.1097/MD.0000000000019000.
6	Dong Y	Efficacy and safety of direct oral anticoagulants versus low-molecular-weight heparinin patients with cancer: a systematic review and meta-analysis.	J Thromb Thrombolysis. 2019 Oct;48(3):400-412. doi: 10.1007/s11239-019-01871-4.
7	Farge D	2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer.	The Lancet Oncology. 20 (10) (pp e566-e581), 2019. Date of Publication: October 2019.
8	Fuentes HE	Direct Oral Factor Xa Inhibitors for the Treatment of Acute Cancer-Associated Venous Thromboembolism: A Systematic Review and Network Meta-analysis.	Mayo Clin Proc. 2019 Dec;94(12):2444-2454. doi: 10.1016/j.mayocp.2019.05.035. Epub 2019 Nov 2.

#	Primary author	Title	Citation
9	Gu ZC	Direct versus conventional anticoagulants for treatmentof cancer associated thrombosis: a pooled and interaction analysis betweenobservational studies and randomized clinical trials.	Ann Transl Med. 2020 Feb;8(4):95. doi: 10.21037/atm.2019.12.152.
10	Kahale LA	Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer.	Cochrane Database of Systematic Reviews. 2018 (6) (no pagination), 2018. Article Number: CD006650. Date of Publication: 18 Jun 2018.
11	Key NS	Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update.	J Clin Oncol. 2020 Feb 10;38(5):496-520. doi: 10.1200/JCO.19.01461. Epub 2019 Aug 5.
12	Kirkilesis GI	Editor's Choice – A Systematic Review and Meta-Analysis of the Efficacy and Safety of Anticoagulation in the Treatment of Venous Thromboembolism in Patients with Cancer.	Eur J Vasc Endovasc Surg. 2019 May;57(5):685-701. doi: 10.1016/j.ejvs.2018.11.004. Erratumin: Eur J Vasc Endovasc Surg. 2019 Dec;58(6):943.
13	Mai V	DOAC compared to LMWH in the treatment of cancer related-venous thromboembolism: a systematic review and meta-analysis.	J Thromb Thrombolysis. 2020 Feb 12. doi: 10.1007/s11239-020-02055-1. [Epub ahead of print]
14	Rossel A	Anticoagulant therapy for acute venous thrombo-embolism in cancer patients:A systematic review and network meta-analysis.	PLoS One. 2019 Mar 21;14(3):e0213940. doi: 10.1371/journal.pone.0213940. eCollection 2019.
15	Sobieraj DM	Anticoagulation for the Treatment of Cancer-Associated Thrombosis: A Systematic Review and Network Meta-Analysis of Randomized Trials.	Clinical and Applied Thrombosis/Hemostasis. 24 (9_suppl) (pp 182S-187S), 2018. Date of Publication: 01 Dec 2018.
16	Vedovati MC	Efficacy and safety of anticoagulant agents in patients with venous thromboembolism and cancer: A network meta-analysis.	Thromb Res. 2018 Oct;170:175-180.doi: 10.1016/j.thromres.2018.08.023. Epub 2018 Sep 1.

17	Wang Y	Efficacy and Safety of Direct Oral Anticoagulants for Secondary Prevention of Cancer-Associated Thrombosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials	Front Pharmacol 2019 Jul 10;10:773. doi: 10.3389/fphar.2019.00773. eCollection 2019.

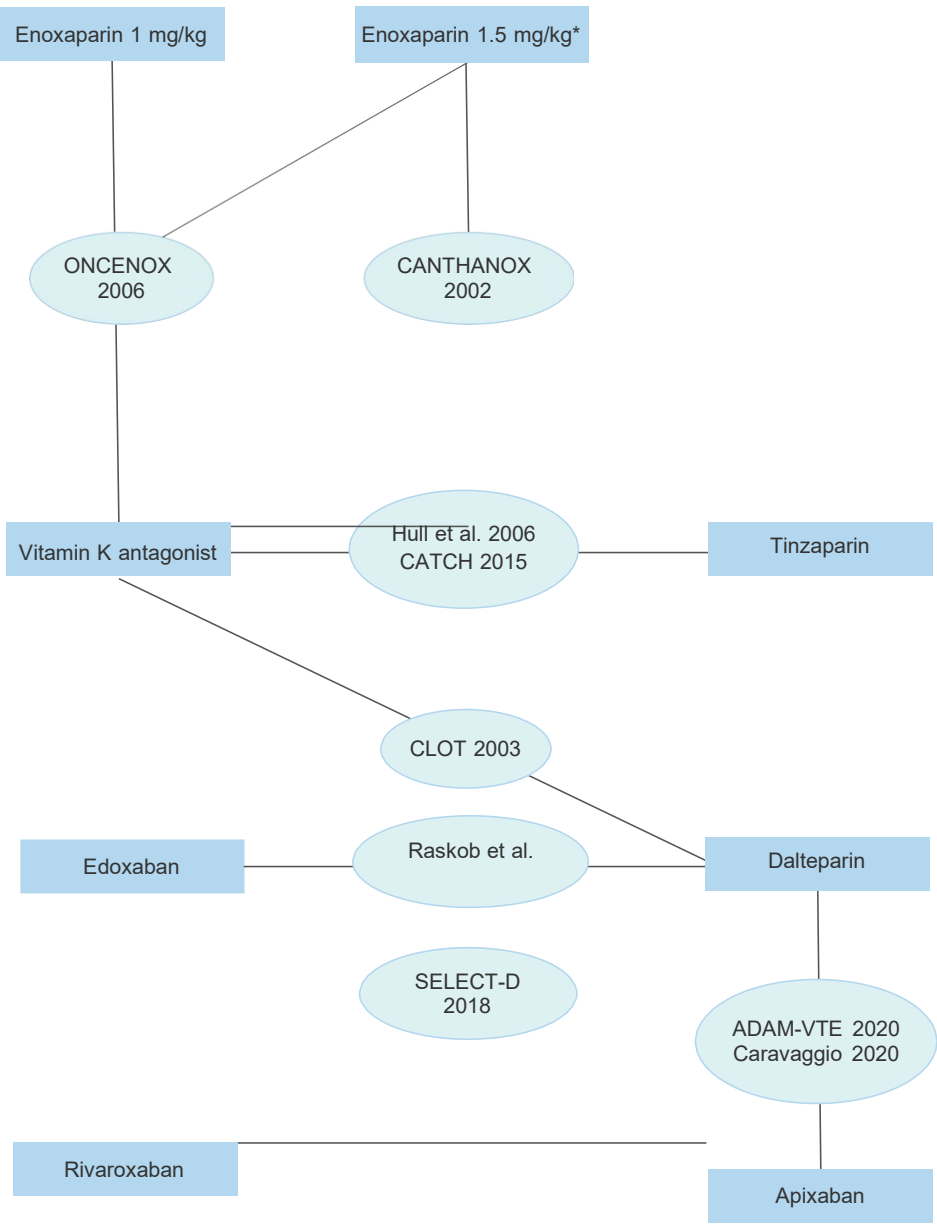
#	Primary author	Title	Citation
		and Prospective Cohort Studies.	
18	Wang Y	Direct oral anticoagulants for thromboprophylaxis in ambulatory patients with cancer.	Hematology. 2020 Dec;25(1):63-70. doi: 10.1080/16078454.2020.1719726.
19	Xing J	Rivaroxaban versus enoxaparin for the preventionof recurrent venous thromboembolism in patientswith cancer: A meta-analysis.	Medicine (Baltimore). 2018 Aug;97(31):e11384. doi: 10.1097/MD.0000000000011384.
20	Yan Y-D	Net clinical benefit of non-vitamin K antagonist oral anticoagulants for venous thromboembolism prophylaxis in patients with cancer: A systematic review and trade- off analysis from 9 randomized controlled trials.	Frontiers in Pharmacology. 9 (JUN) (no pagination), 2018. Article Number: 575. Date of Publication: 12 Jun 2018.
21	Yang M	Comparison between direct factor Xa inhibitors and low-molecular-weight heparin for efficacy and safety in the treatment of cancer-associated venous thromboembolism: A meta-analysis.	J Cancer Res Ther. 2019;15(7):1541-1546. doi: 10.4103/jcrt.JCRT_68_19.
22	Zeng J	Efficacy and Safety of Direct Oral Anticoagulants for Risk of Cancer-Associated Venous Thromboembolism.	Clin Appl Thromb Hemost. 2019 Jan-Dec;25:1076029619853629. doi: 10.1177/1076029619853629.
23	Zhang M	Do lung cancer patients require routine anticoagulation treatment? A meta-analysis.	The Journal of international medical research. 48 (1) (pp 300060519896919), 2020. Date of Publication: 01 Jan 2020.
24	Mulder	Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis	Blood. (no pagination), 2020. Date of Publication: 12 May 2020.
25	Frere	Are Patients with Active Cancer and Those with History of Cancer Carrying theSame Risks of Recurrent VTE and Bleeding While on Anticoagulants?	Cancers. 12 (4) (no pagination), 2020. Article Number: 917. Date of Publication: April 2020.
26	Giustozzi	Direct Oral Anticoagulants for the Treatment of Acute Venous Thromboembolism Associated with Cancer: A Systematic Review and Meta-Analysis	Thrombosis and haemostasis. (no pagination), 2020. Date of Publication: 04 May 2020.

#	Primary author	Title	Citation
27	Tao	The efficacy and safety of DOACs versus LMWH for cancer-associated thrombosis: A systematic review and meta-analysis	European journal of haematology. (no pagination), 2020. Date of Publication: 22 May 2020.
28	Moik	Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: Updated systematic review and meta-analysis of randomized controlled trials	Research and Practice in Thrombosis and Haemostasis. (no pagination), 2020. Date of Publication: 2020.
29	Ueyama	Network meta-analysis of anticoagulation strategies for venous thromboembolism in patients with cancer.	Journal of Thrombosis and Thrombolysis. (no pagination), 2020. Date of Publication: 2020.
30	Jara-Palomares	Tinzaparin in cancer associated thrombosis beyond 6 months: TiCAT study	Thrombosis Research 157 (2017) 90–96
31	Francis	Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study	Journal of Thrombosis and Haemostasis, 13: 1028–1035

Randomized controlled trials (published January 1, 2018–June 7, 2020)

#	Primary author	Title	Citation
RCT1	Agnelli G	Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer	N Engl J Med. 2020 Apr 23;382:1599-1607
RCT2	Kraaijpoel N	Clinical Impact of Bleeding in Cancer- Associated Venous Thromboembolism: Resultsfrom the Hokusai VTE Cancer Study	Thromb Haemost. 2018 Aug;118(8):1439-1449. doi: 10.1055/s-0038-1667001. Epub 2018 Jul 30
RCT3	McBane RD	Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial	J Thromb Haemost. 2020 Feb;18(2):411-421. doi: 10.1111/jth.14662. Epub 2019 Nov 28.
RCT4	Raskob GE	Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism	N Engl J Med. 2018 Feb 15;378(7):615-624. doi: 10.1056/NEJMoa1711948. Epub 2017 Dec 12.

Appendix 5. Network Diagram of Active Comparator RCTs



* Titrate to 1 mg/kg after 5 days

Appendix 6. Cost-Effectiveness Literature Search Strategy

Concept 1: LMWHs OR DOACs

exp Heparin, Low-Molecular-Weight/
Low Molecular Weight Heparin/
Dalteparin/ OR Enoxaparin/ OR Nadroparin/ OR Tinzaparin/
(low molecular weight heparin? OR LMWH?).tw,kf,kw.
(dalteparin* OR Tedelparin OR FR-860 OR FR860 OR Kabi-2165 OR Kabi2165 OR Fragmin? OR enoxaparin* OR PK10169 OR PK-10169 OR EMT-967 OR EMT967 OR Lovenox OR Clexane OR EMT-966 OR EMT966 OR nadroparin* OR Fraxiparin? OR CY-216 OR CY216 OR tinzaparin* OR Innohep).tw,kf,kw.
Factor Xa Inhibitors/ OR ((direct* ADJ2 oral ADJ (anti-coagulant? OR anticoagulant?)) OR DOAC? OR direct factor xa inhibitor?).tw,kf,kw.
Apixaban/ OR Dabigatran/ OR Edoxaban/ OR Rivaroxaban/
(apixaban* OR BMS-562247 OR BMS562247 OR dabigatran* OR BIBR 1048 OR Pradaxa* OR edoxaban* OR Savaysa* OR DU-176? OR rivaroxaban* OR Xarelto* OR BAY 59-7939 OR BAY 597939).tw,kf,kw,nm.

Concept 2: VTE (DVT/PE)

exp Venous Thromboembolism/ OR (venous thromboembolism? OR venous thrombo-embolism? OR VTE?).tw,kf,kw.
exp Venous Thrombosis/ OR (deep vein thrombos#s OR DVT? OR phlebothrombos#s OR venous thrombos#s).tw,kf,kw.
Pulmonary Embolism/ OR ((lung? OR pulmonary) ADJ2 (embolism? OR embolization OR embolus OR emboly OR micro-embol* OR microembol* OR thrombo-embol* OR thromboembol*)).tw,kf,kw.

Concept 3: Cancer

exp Neoplasms/ OR exp Neoplasm/ OR (cancer* OR carcinoma* OR neoplasm* OR tumour* OR tumor* OR adeno-carcinoma* OR adenocarcinoma*).tw,kf,kw.

Filter: Cost-Effectiveness

*Economics/
exp *"Costs and Cost Analysis"/
exp *Health Economics/
(economic ADJ2 model*).mp.
(cost minimi* OR cost-utilit* OR health utilit* OR economic evaluation* OR economic review* OR cost outcome OR cost analys?s OR economic analys?s OR budget* impact analys?s).tw,kf,kw.
(cost-effective* OR pharmacoeconomic* OR pharmaco-economic* OR cost-benefit OR costs).ti,kf,kw.
(life year OR life years OR qaly* OR cost-benefit analys?s OR cost-effectiveness analys?s).ab,kf,kw.
(cost OR economic*).ti,kf,kw. and (costs OR cost-effectiveness OR markov).ab.
Ovid
Database(s): Embase 1974 to 2020 July 06, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy

#	Searches	Results
1	exp Heparin, Low-Molecular-Weight/	75291
2	Low Molecular Weight Heparin/	46765
3	Dalteparin/ or Enoxaparin/ or Nadroparin/ or Tinzaparin/	36234
4	(low molecular weight heparin? or LMWH?).tw,kf,kw.	35061
5	(dalteparin* or Tedelparin or FR-860 or FR860 or Kabi-2165 or Kabi2165 or Fragmin? or enoxaparin* or PK10169 or PK-10169 or EMT-967 or EMT967 or Lovenox or Clexane or EMT-966 or EMT966 or nadroparin* or Fraxiparin? or CY-216 or CY216 or tinzaparin* or Innohep).tw,kf,kw.	21625
6	Factor Xa Inhibitors/ or ((direct* adj2 oral adj (anti-coagulant? or anticoagulant?)) or DOAC? or direct factor xa inhibitor?).tw,kf,kw.	18877
7	Apixaban/ or Dabigatran/ or Edoxaban/ or Rivaroxaban/	31200
8	(apixaban* or BMS-562247 or BMS562247 or dabigatran* or BIBR 1048 or Pradaxa* or edoxaban* or Savaysa* or DU-176? or rivaroxaban* or Xarelto* or BAY 59-7939 or BAY 597939).tw,kf,kw,nm.	28892
9	or/1-8	122020
10	exp Venous Thromboembolism/ or (venous thromboembolism? or venous thrombo-embolism? or VTE?).tw,kf,kw.	185394
11	exp Venous Thrombosis/ or (deep vein thrombos#s or DVT? or phlebothrombos#s orvenous thrombos#s).tw,kf,kw.	220136
12	Pulmonary Embolism/ or ((lung? or pulmonary) adj2 (embolism? or embolization or embolus or emboly or micro-embol* or microembol* or thrombo-embol* or thromboembol*)).tw,kf,kw.	132658
13	or/10-12	364385
14	exp Neoplasms/ or exp Neoplasm/ or (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or adeno-carcinoma* or adenocarcinoma*).tw,kf,kw.	9596939
15	*Economics/	35764
16	exp *"Costs and Cost Analysis"/	150393
17	exp *Health Economics/	255140
18	(economic adj2 model*).mp.	20628
19	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).tw,kf,kw.	83259
20	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kf,kw.	179961
21	(life year or life years or qaly* or cost-benefit analys?s or cost-effectivenessanalys?s).ab,kf,kw.	77156
22	(cost or economic*).ti,kf,kw. and (costs or cost-effectiveness or markov).ab.	147801
23	or/15-22	567778
24	9 and 13 and 14 and 23	171
25	limit 24 to english language	167
26	limit 25 to yr = "2018-Current"	48
27	remove duplicates from 26	36

Google

(low molecular weight heparin OR Dalteparin OR Enoxaparin OR Nadroparin OR Tinzaparin OR direct oral anti-coagulant OR direct oral anticoagulant OR Apixaban OR Dabigatran OR Edoxaban OR Rivaroxaban) + CE filter + geographic/disease terms