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Anticoagulation for the Treatment of Cancer-Associated Thrombosis: A Systematic Review and Network Meta-Analysis of Randomized Trials

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Abstract

To perform a systematic review and network meta-analysis evaluating the efficacy and safety of low-molecular-weight heparins (LMWHs), vitamin K antagonists (VKAs), and direct-acting oral anticoagulants (DOACs) for the treatment of cancer-associated thrombosis (CAT). We searched MEDLINE, Cochrane Central Register of Controlled Trials, and conference abstracts through March 2018. Randomized controlled trials (RCTs) enrolling adults with CAT comparing 2 or more full-dose anticoagulants (LMWH, VKA, and DOAC) and evaluating recurrent venous thromboembolism (VTE), major bleeding, and/or all-cause mortality were included. Reviewers identified studies, extracted data, and assessed the quality of the evidence in duplicate. A frequentist network meta-analysis, which uses direct and indirect evidence to simultaneously compare multiple interventions, was performed using a random-effects approach. Results are reported as pooled relative risks (RRs) with 95% confidence intervals (CIs). We included 13 RCTs (n = 6292): 7 compared LMWHs with VKAs, 4 compared DOACs with VKAs, and 2 compared DOACs with LMWHs. The risk of recurrent VTE was significantly reduced by 28% and 54% with a DOAC compared to an LMWH and a VKA, respectively. Low-molecular-weight heparins significantly reduced the risk of recurrent VTE by 36% versus VKAs. The risk of major bleeding was 14% higher with DOACs compared to LMWHs and 15% and 25% lower with DOACs and LMWHs versus VKAs, although 95% CIs included unity for each. The risk of all-cause mortality appeared similar for all 3 comparisons (RR = 1.0 for each comparison). Direct-acting oral anticoagulants appeared superior in reducing recurrent VTE in patients with CAT compared to LMWH and VKAs, but an increased risk of major bleeding versus LMWH cannot be ruled out.

Keywords

anticoagulants, venous thromboembolism, bleeding

Introduction

Active cancer increases a patients' risk of venous thromboembolism (VTE) up to 7-fold compared to age-matched controls, corresponding to about 1 thrombotic event per 200 active patients with cancer annually.[1-3] For this reason, management of cancer-associated thrombosis (CAT) with anticoagulation is recommended by guidelines,[4-8] but its use is complicated by a delicate balance between patients' high risk of recurrent VTE and bleeding.[3,9] Current CAT treatment guidelines preferentially recommend low-molecular-weight heparins (LMWHs) as first-line treatment for CAT, with oral anticoagulants such as vitamin K antagonists (VKAs) and direct-acting oral anticoagulants (DOACs) reserved for patients unable or unwilling to use long-term parenteral therapy.[4-8]

Randomized controlled trials (RCTs) comparing LMWHs and oral anticoagulants for the treatment of CAT have been performed, with a particular focus in recent years on DOACs because of their ease of use. To better understand the comparative efficacy and safety of LMWHs, VKAs, and DOACs for the

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treatment of CAT, we performed a systematic review and network meta-analysis of available RCT evidence.

Methods

This report conforms to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement for network meta-analyses.[10]

Literature Search

We searched MEDLINE and the Cochrane Central Register of Controlled Trials via OVID from their earliest date through March 2018. The search strategy included medical subject heading and key words for the LMWH, VKAs, DOACs, and CAT (eAppendix). Citations were limited to those published in English. A manual search of references from reports of clinical trials and review articles was also conducted to identify additional relevant citations. We also performed a manual search of proceedings from related conferences (International Society on Thrombosis and Haemostasis, American Society of Hematology, American Society of Clinical Oncology, European Society for Medical Oncology, Thrombosis and Hemostasis Societies of North America, International Conference on Thrombosis and Hemostasis Issues in Cancer) from the past year.

Study Selection

We included data from RCTs that enrolled adults (≥18 years) with CAT that compared at least 2 full-dose anticoagulants (LMWH, VKA, and DOAC). Studies were required to report at least one of the following outcomes: recurrent VTE, major bleeding, and/or all-cause mortality. Identified titles and abstracts were screened for eligibility by 2 independent investigators. For those citations satisfying eligibility criteria, the full-text publication was retrieved and screened.

Data Extraction and Risk of Bias Assessment

Data were abstracted into a standardized collection form by one investigator and verified by a second. Data collected from each study included author, year of publication, study design, duration of patient follow-up, sample size, active cancer definition, cancer sites, anticoagulant dosing, pertinent patient characteristics, and end point definition and incidence. Risk of bias for each study was independently assessed by 2 investigators using The Cochrane Collaboration Risk of Bias Tool for RCTs[11] (eAppendix in Supplemental Materials). The evaluated domains included random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other sources of bias. We evaluated the following parameters under "other sources of bias": use of validated definitions for VTE, major bleeding, and active cancer; reporting of cancer severity and study design to account for patients with cancer (eg, stratified randomization).

Data Synthesis and Analysis

We performed a network meta-analysis for each outcome within a frequentist framework. We implemented a random-effects model assuming common heterogeneity across all comparisons and calculated a relative risk (RR) and associated 95% confidence interval (CI). Statistical heterogeneity within the network was assessed by calculating the heterogeneity variance parameter (τ^2). Inconsistency was assessed by statistically comparing the results from direct and indirect estimates. The ranking of treatments for each outcome was performed using the P score (the probability that one treatment is better than the others), with higher values corresponding to a higher ranking.[12] The rankings for recurrent VTE, major bleeding, and all-cause mortality were combined in an Haase diagram, which illustrates treatment relations in a partially ordered set with superior objects located above inferior ones.[13] Treatments not connected by arrows are considered incomparable, as individual rankings may go in opposite directions.

We also performed traditional meta-analyses for each outcome with a $P < .05$ considered statistically significant. Separate analyses were performed for each anticoagulation pairing, combining data from approved doses of the same therapies. For each outcome, the RR and associated 95% CIs were calculated using a random-effects model and inverse-variance weighting. We assessed for presence of statistical heterogeneity using the Cochrane P value ($P < .10$ significant) and the I^2 statistic which represents the percentage (0%-100%) of variability in the treatment estimate that is attributable to heterogeneity.[14] We planned to assess for small study effects (including publication bias) using funnel plot inspection and tests of plot asymmetry when 10 or more trials were pooled.[15] However, none of the pooled analyses reached this threshold. All analyses were performed using the 'netmeta' (version 0.9-8) or 'meta' (version 3.4.4) packages in R version 3.4. (The R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 13 studies[3,4,16-26] met inclusion criteria (Figure 1, eTable 1 and eFigure 1 in Supplemental Materials). Nine studies were RCTs performed exclusively in patient with active cancer.[3,4,17,20,22-24,26] Seven RCTs compared LMWH with VKA,[3,4,19,21-23,25] and 2 RCTs compared a DOAC with LMWH.[16,17] Two studies were subgroup analyses of patients with cancer from the larger primary RCTs Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) and Hokusai VTE, comparing apixaban and edoxaban with a parenteral anticoagulant bridged to a VKA, respectively.[25,26] Two studies were pooled analysis of the subgroup of patients enrolled with cancer in "sister" RCTs; EINSTEIN DVT and EINSTEIN PE evaluating rivaroxaban and RECOVER I and RECOVER II evaluating dabigatran, both in comparison with a parenteral anticoagulant bridged to VKA.[19,23] All trials treated patients for a minimum of 3 months, 3 trials allowed up to 12 months of

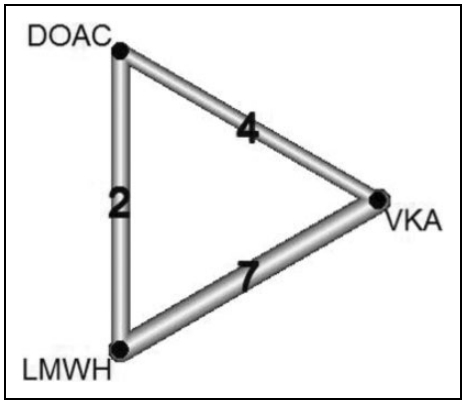

Figure 1. Network diagram. Each node represents a treatment in the network, with the thickness of the line corresponding to the proportion of direct evidence between the treatments. The number corresponds to the quantity of direct-evidence trials. DOAC indicates direct-acting oral anticoagulant; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.

treatment, but most trials (62%) treated for a fixed durations of 6 months. Cancer histology was diverse including solid and hematologic malignancies. Metastatic cancer frequency and antineoplastic treatment ranged from 13%[19] to 67%[3] and 29%[23] to 78%,[3] respectively.

Risk of bias across the domains of random sequence generation, allocation concealment, blinding of outcome assessment, incomplete data reporting, and selective outcome reporting was ranked low for most trials, with a few instances where risk of bias was unclear (eFigure 2 in Supplemental Material). Ten studies were ranked with high risk of bias in the domain of participant and personnel blinding given the open-label design common to CAT trials they employed.[3,4,16-18,20-24] Ascertainment of severity of cancer was assessed to have high risk of bias in 8 trials due to a lack of reporting of either cancer stage or Eastern Cooperative Oncology Group performance status.[18-20,22-26] Finally, because some of the included trials were subgroup analyses of all-comer VTE trials without stratified randomization of active cancer at baseline, these data sources were scored as having a higher risk of bias for this domain.[20,23-25]

Upon network meta-analysis (Figure 2, eFigures 3-5 in Supplemetal Material), DOACs reduced the risk of VTE recurrence by 28% compared to LMWH (RR: 0.72 [0.55-0.96]) and 54% compared to VKAs (RR: 0.46 [0.34-0.62]). Low-molecular-weight heparin significantly reduced the risk of VTE recurrence by 36% compared to VKA (RR: 0.64 [0.50-0.81]). No significant statistical heterogeneity was seen in the VTE model ($\tau^2 = 0$). The risk of major bleeding was higher with DOACs versus LMWH (RR: 1.14 [0.64-2.03]) and lower with DOACs (RR: 0.85 [0.49-1.48]) or with LMWHs (RR: 0.75 [0.46-1.22]) versus VKAs, although statistical significance was not reached for these comparisons. Little statistical heterogeneity was seen in the major bleeding model ($\tau^2 = 0.17$). All-cause mortality risk was unchanged for all comparisons ($\tau^2 = 0$).

Review of *P* scores indicate that DOACs were ranked highest for VTE risk reduction (*P* score = .99), LMWHs were ranked highest for favorable major bleeding risk (*P* score = .78), and the 3 anticoagulant classes were comparable in rank for the outcome of all-cause mortality (Figure 3A). Considering the network meta-analysis results for recurrent VTE, major bleeding, and mortality, the Hasse diagram (Figure 3B) indicates DOACs and LMWH, are superior to VKAs although they are incomparable to each other.

Direct and indirect evidence were consistent within the networks for VTE recurrence ($P = .24$) and mortality ($P = .43$). Although direct and indirect estimates for major bleeding were opposing in direction of effect when DOACs were compared to LMWHs or VKAs, statistically significant inconsistency was not detected ($P \geq .09$). For all pair-wise comparisons using traditional meta-analysis, there were no cases of statistically significant heterogeneity ($P < .10$ for all comparisons), and I^2 values were 0% for all but 2 analyses: LMWH versus VKA for major bleeding ($I^2 = 33\%$) and DOAC versus LMWH for all-cause mortality ($I^2 = 50\%$).

A

DOAC	0.72 (0.56 to 0.96)	0.46 (0.34 to 0.62)
1.38 (1.04 to 1.84)	LMWH	0.64 (0.50 to 0.81)
2.18 (1.61 to 2.94)	1.57 (1.23 to 2.01)	VKA

B

DOAC	1.14 (0.64 to 2.03)	0.85 (0.49 to 1.48)
0.88 (0.49 to 1.56)	LMWH	0.75 (0.46 to 1.22)
1.17 (0.67 to 2.03)	1.34 (0.82 to 2.17)	VKA

C

DOAC	1.04 (0.90 to 1.19)	0.92 (0.72 to 1.18)
1.00 (0.89 to 1.14)	LMWH	1.02 (0.90 to 1.15)
1.00 (0.86 to 1.17)	1.00 (0.89 to 1.12)	VKA

Figure 2. Results of the network meta-analysis. Results for recurrent VTE (A), major bleeding (B), and all-cause mortality (C) are shown as relative risk and 95% confidence intervals. The boxes in gray represent the represent changes in the row-defining treatment versus those in the column-defining treatment (referent). The boxes in white represent changes in the column-defining treatment versus those in the row-defining treatment (referent). Significant results are underscored. VTE indicates venous thromboembolism.

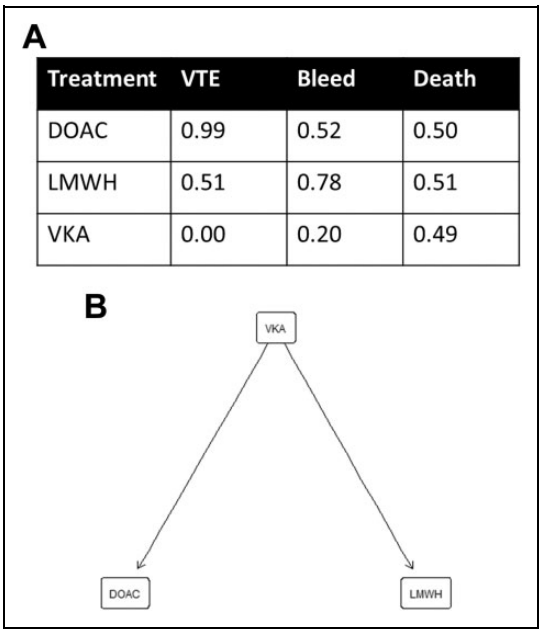

Figure 3. Ranking of treatments. The *P* score (A) represents the probability that one treatment is better than the others, with higher values (ranging from 0 to 100) corresponding to a higher ranking. The Haase diagram (B) illustrates treatment relations in a partially ordered set with superior objects located above inferior ones. The treatments on the top of the diagram have a higher overall rank than the treatments below them, with arrows pointing to the inferior treatments. Treatments not connected by arrows are considered incomparable, as individual rankings go in opposite directions. DOAC indicates direct-acting oral anticoagulant; LMWH, low molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Discussion

This network meta-analysis suggests that LMWHs and DOACs are more effective and safer anticoagulants for CAT compared to VKAs. Direct-acting oral anticoagulants appeared superior in reducing VTE recurrence compared to LMWH which has been the preferred anticoagulant in patients with cancer, since the CLOT trial demonstrated superiority of dalteparin over warfarin[3,6,8,27] Our analysis cannot rule out an increased risk of major bleeding with DOACs compared to LMWHs. We did not find differing effects of anticoagulants on all-cause mortality. This is not surprising as prior data suggest that most deaths in CAT are due to cancer progression rather than VTE complications.[3]

Our analysis reflects the most current summary of evidence in the field regarding the potential role of DOACs in CAT, which to date have been inconsistently recommended within treatment guidelines. The American Society of Clinical Oncology recommends against DOACs (due to insufficient evidence at the time of guideline writing).[6] The American College of Chest Physicians (ACCP), although stating oral anticoagulants are an option when LMWH is not suitable, do give preference to either DOAC or VKA therapy.[8] Like ACCP, the International Initiative of Thrombosis in Cancer also suggests oral anticoagulants when a LMWH is not suitable but recommends DOACs as an alternate to VKAs only in patients who are stable and not receiving chemotherapy.[27] Regardless, real-world data show that DOACs are being prescribed for up to one-fifth of patients with CAT.[28] This perhaps may be because of the convenience of DOACs in comparison to LMWHs or VKAs. In Hokusai-VTE, cancer treatment discontinuation with LMWH was higher than with edoxaban (completed 12 months of therapy 29% for LMWH versus 38% with edoxaban) with patient inconvenience (15% vs 4%) and discontinuation after physicians' benefit–risk judgement (9% vs 6%) being the main reasons for stopping anticoagulant therapy.[16]

The choice of anticoagulation for CAT treatment, particularly between an LMWH and DOAC, should take into account an individual patients' risks of both thrombosis and bleeding. Certain cancer types, such as mucin producing tumors, have been shown to be associated with higher thrombogenicity. Moreover, metastatic disease, more advanced clinical stage, and treatment with chemotherapy or antiangiogenic agents can also increase risk of thrombosis of patients with cancer.[5,29] Bleeding risk is inherently higher in patients with cancer[30] and is further elevated due to the need for invasive diagnostic or therapeutic procedures and the development of thrombocytopenia secondary to malignancy or chemotherapy.[5] Fear of bleeding complications is often elevated in patients with brain tumors due to concerns regarding the risk of intracranial hemorrhage.[31] Subgroup analysis from the Hokusai-VTE cancer study[16] suggest that patients with gastrointestinal, colorectal, and esophageal cancers were more likely to develop major bleeds on edoxaban compared to dalteparin, while the hazard of developing a major bleed appeared similar between the 2 agents in patients with other cancer locations. Finally, it should be noted that clinically relevant bleeding is a frequent cause of anticoagulation therapy interruption or discontinuation potentially reestablishing patients' VTE risk.[32]

Real-world studies provide further support for the findings of our network meta-analysis.[32,33] Streiff and colleagues[33] evaluated 2428 patients with active cancer in a longitudinal cohort analysis (of which 707 were treated with rivaroxaban, 660 with LMWH, and 1061 with warfarin). The risk of VTE recurrence was observed to be lower with rivaroxaban versus either an LMWH (hazard ratio [HR]: 0.72, 95% CI: 0.52-0.95, $P = .024$) or warfarin (HR: 0.74, 95% CI: 0.56-0.96, $P = .028$). The risk of major bleeding did not differ across treatments, with incidences ranging from 8.2% to 9.0%. A cohort study by Simmons et al[32] evaluated 266 patients in an anticoagulant clinic registry, 98 (36.8%) of which were treated with rivaroxaban and the remainder with enoxaparin. Risk of VTE recurrence (1.0% vs 4.2%, $P = .15$), major bleeding (5.1% vs 3.6%, $P = .55$), and all-cause mortality (4.1% vs 8.9%, $P = .14$) were not found to differ between treatments at 3 months, and these findings remained consistent through 12 months.

There are several strengths to this analysis that enhance applicability of our results. Inclusion criteria required drug doses to be those commonly employed for CAT such that regimens of once-daily LMWH were excluded. Studies included a range of malignancies, including those associated with the highest

thrombosis risk. Several trials also included a high proportion of metastatic cancers and those on chemotherapy, further enhancing applicability to subgroups of patients with cancer having high VTE risk. However, there are some limitations to our analysis that should be considered. First, we included CAT sub-analyses of all-comer VTE trials into our meta-analysis. Next, we were unable to evaluate outcomes in cancer subtypes due to sparse reporting of these subgroup analyses in included RCTs. Such additional analysis would be helpful in further informing patient-specific treatment decisions. Finally, our network meta-analysis aimed to compare efficacy and safety of LMWHs, DOACs, and VKAs in the treatment of CAT but was not able to assess the optimal duration of anticoagulation therapy in this population. The majority of trials evaluated a fixed 6-month duration of anticoagulation, but some studies allowed treatment for up to 12 months at the discretion of the treating clinician. It therefore is unclear whether the relative risks and benefits of evaluated anticoagulants would differ if utilized for longer (or shorter) treatment durations.

Conclusions

Our network meta-analysis suggests DOACs may reduce the risk of recurrent VTE compared to LMWHs and VKAs in CAT. Both LMWHs and DOACs appear to reduce the risk of recurrent VTE versus a VKA without increasing major bleeding risk. An increase in major bleeding risk with a DOAC compared to an LMWH was observed, but 95% CIs were wide.

Authors' Note

Institutional review board approval was not required for this research.

Author Contributions

Dr Coleman had full access to all of the data in this study and take responsibility for the integrity of the data, and accuracy of the data analysis; and contributed to concept and design. Coleman, Baker, Sobieraj, Smith, Sasiela, Trexler, and Kim contributed to acquisition, analysis, or interpretation of data. Coleman, Baker, and Sobieraj contributed in drafting of the manuscript. Coleman, Baker, Sobieraj, Smith, Sasiela, Trexler, and Kim contributed in critical revision of the manuscript for important intellectual content. Coleman, Baker, and Sobieraj contributed in statistical analysis.

Declaration of Conflicting Interests

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Supplemental Material

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References

1. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Risk factors for deep vein thrombosis and pulmonary embolism. *Arch Intern Med*. 2000;160(6):809-815.
2. Bloom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations and the risk of venous thrombosis. *JAMA*. 2005;293(6):715-722.
3. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003; 349(2):146-153.
4. Lee AY, Kamphuisen PW, Meyer G, et al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA*. 2015;314(7): 677-686.
5. Lee AY, Peterson EA. Treatment of cancer-associated thrombosis. *Blood*. 2013;122(14):2310-2317.
6. Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice guideline update 2014. *J Clin Oncol*. 2015;33(6):654-656.
7. Bach M, Bauersachs R. Spotlight on advances in VTE management: CALLISTO and EINSTEIN CHOICE. *Thromb Haemost*. 2016;116(suppl 2):S24-S32.
8. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315-352.
9. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thromboembolism. *Blood*. 2002;100(10):3484-3488.
10. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analysis of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777-784.
11. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(7829):d5928.
12. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. 2015;15:58.
13. Rucker G, Schwarzer G. Resolve conflicting rankings of outcomes in network meta-analysis: partial ordering of treatments. *Res Synth Methods*. 2017;8(4):526-536.
14. Higgins JP, Thomas SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315(7109):629-634.
16. Raskob GE, Es NV, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378(7):615-624.

17. Young AM, Marshall A, Ehirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017-2023.
18. Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med*. 2006;119(12):1062-1072.
19. Schulman S, Goldhaber SZ, Kearon C, et al. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. *Thromb Haemost*. 2015;114(1):150-157.
20. Romera A, Cairols MA, Vila-Coll R, et al. A randomized open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. *Eur J Endovasc Surg*. 2009; 37(3):349-356.
21. Deitcher SR, Kessler CM, Merli G, et al. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for 180-day period. *Clin Appl Thromb Hemost*. 2006;12(4):389-396.
22. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer. *Arch Intern Med*. 2002;162(15):1729-1735.
23. Prins MH, Lensing AW, Brighton TA, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomized controlled trials. *Lancet Haematol*. 2014; 1(1):e37-e46.
24. Lopez-Beret P, Orgaz A, Fontcuberta J, et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. *J Vasc Surg*. 2001;33(1):77-90.
25. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Heamost*. 2015;13(12): 2187-2191.
26. Raskob GE, van Es N, Segers A, et al. Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomized, double-blind, double-dummy trial. *Lancet Heamatol*. 2016;3(8): e379-e387.
27. Farge D, Bounameauxz H, Brenner B, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2016;17:e452-e466.
28. Khorana AA, Yannicelli D, McCrae KR, et al. Evaluation of US prescription patterns: are treatment guidelines for cancer-associated venous thromboembolism being followed? *Thromb Res*. 2016;145:51-53.
29. Lee AYY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. *Circulation*. 2003;107(23 suppl 1):I17-I21.
30. Prandoni P, Trujillo-Santos J, Surico T, et al. Recurrent thromboembolism and major bleeding during oral anticoagulant therapy in patients with solid cancer: findings from the RIETE registry. *Haematologica*. 2008;93(9):1432-1434.
31. Chai-Adisaksopha C, AlKindi SY, Cheah M, et al. Outcomes of low-molecular-weight heparin treatment for venous thromboembolism in patients with primary and metastatic brain tumors. Paper presented at: 2015 ASH Annual Meeting; Orlando, FL, December 7, 2015. Abstract 428.
32. Simmons B, Wysokinski W, Saadig RA, et al. Efficacy and safety of rivaroxaban compared to enoxaparin in treatment of cancer associated venous thromboembolism [published online April 4, 2018]. *Eur J Haematol*. 2018. doi: 10.1111/ejh.13074.
33. Streiff MB, Milentijevic D, McCrae K, et al. Effectiveness and safety of anticoagulants for the treatment of venous thromboembolism in patients with cancer. *Am J Hematol*. 2018;93(5):664-671.