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Net clinical benefit of DOACs vs. usual anticoagulation treatment in venous thromboembolism and active cancer: systematic review and meta-analysis

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Abstract

Patients with active cancer are at high risk of recurrent venous thromboembolism (VTE). Usual treatment includes low molecular weight heparin (LMWH), while vitamin K antagonists (VKAs) have also been used as substitutes for LMWH. Direct oral anticoagulants (DOACs) are considered a beneficial alternative to the usual treatment but are accompanied by an increased rate of bleeding compared to LMWH. We conducted a meta-analysis to evaluate the benefits and harms under a common denomination, namely the net clinical benefit (NCB), between DOACs and usual anticoagulation. The primary outcome was NCB-1, defined as non-fatal VTE, major non-fatal bleedings, and all-cause mortality). Co-primary outcomes were 1) NCB-2 (i.e., NCB-1 and clinically relevant non-major bleedings) and 2) NCB-3 (i.e., fatal or non-fatal VTE and major bleedings). A random-effects model was used to calculate outcome risk ratios and 95% confidence intervals (CI). Prospective Register of Systematic Reviews identification number CRD42021284238. We selected 8 studies (n = 4,4461 patients; mean follow-up, 6 months). The NCB-1 and -2 were not different between DOACs and usual anticoagulation, while the NCB-3 showed a reduction of 28% (95% CI, 10–42%), favoring DOACs. Recurrent VTE was reduced by 40% (95% CI, 25–53%) with DOACs than the usual treatment. Different bleeding outcomes and all-cause mortality were not different between treatments. All primary outcomes did not differ between DOACs and LMWH, while NCB-2 and NCB-3 were reduced with DOACs than VKAs**.** The NCB of DOACs was similar or more favorable to usual anticoagulation in patients with active cancer due to a substantial reduction of VTE and no bleeding excess.

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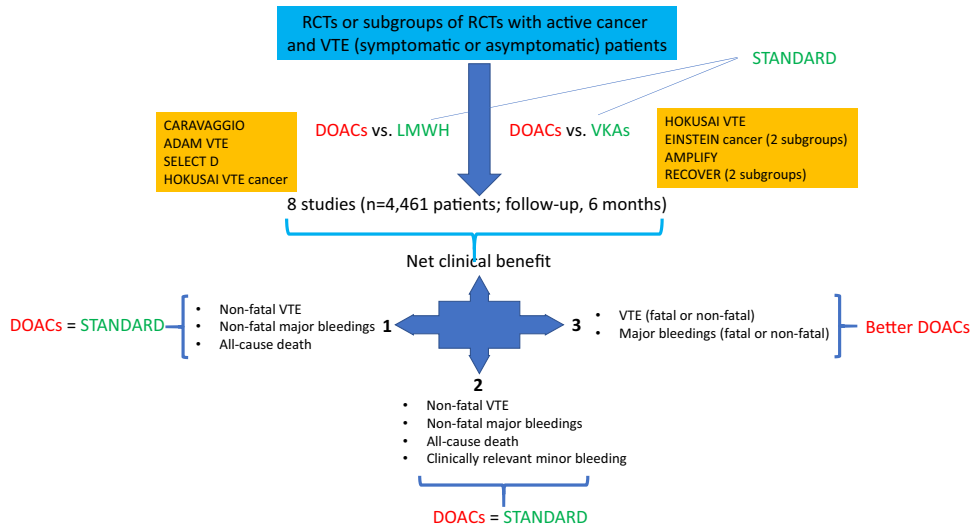
Graphical Abstract



Keywords Cancer · Venous thromboembolism · Pulmonary embolism · Deep venous thrombosis · DOACs

Abbreviations

CI	Confidence interval
DOACs	Direct oral anticoagulants
ISTH	International society on thrombosis and hemostasis
GRADE	Grading of recommendations, assessment, development, and evaluation
LMWH	Low-molecular-weight heparin
NCB	Net clinical benefit
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	Prospective register of systematic reviews
RCTs	Randomized controlled trials
Rob2	Revised Cochrane risk of bias tool
VKAs	Vitamin K antagonists
VTE	Venous thromboembolism

Highlights

- The net clinical benefit of direct anticoagulants is similar or more favorable to standard anticoagulation in patients with active cancer due to a substantial reduction of venous thromboembolism and no excess in bleedings
- The anticoagulation treatment should be individualized in patients with active cancer. Thus, low molecular weight heparin may occasionally be preferred over direct anticoagulants.
- Vitamin K antagonists proved less beneficial in terms of a net clinical benefit than direct anticoagulants. However, their use may be reserved for special clinical indications or whenever the use of direct anticoagulants or low molecular weight heparin is limited because of socio-economical barriers.

Introduction

Patients with active cancer are prone to developing venous thromboembolism (VTE), with higher rates of recurrence and bleeding complications when treated with vitamin K antagonists (VKAs) than with low-molecular-weight heparin (LMWH) [1–3]. However, daily subcutaneous injection of anticoagulant treatment for at least six months, as recommended by the guidelines [1, 2], negatively impacts the quality of life in cancer patients and may be non-affordable by economic means for health care systems or the individual patient. Thus, after a short course with LMWH, direct oral anticoagulants (DOACs) are used [1, 2] despite the increased rate of bleeding because of interactions with chemotherapy agents or surgical procedures [3]. Also, regarding LMWH, there is a lack of evidence supporting that the beneficial effects are extended over six months [1, 2], while their use may be limited by the economic burden, especially in low-income countries. However, more recent guidelines based on moderate evidence suggest that anticoagulation treatment may be extended over six months [4, 5].

In clinical trials for the secondary prevention of VTE [1, 2], the implemented DOACs were either the inhibitors of activated factor X (i.e., edoxaban, apixaban, and rivaroxaban) or the direct inhibitor of activated factor II (i.e., dabigatran). The main mechanistic advantages of DOACs vs. VKAs are (1) direct suppression of key plasma proteases vs. indirect coagulation inhibition through vitamin K-dependent factors, (2) convenience of use because of a standard daily dose vs. difficulties of use because of a variable daily dose, (3) minor vs. major drug and food interactions, (4) wide vs. narrower therapeutic window, and (5) no need of vs. mandatory laboratory monitoring [1, 2, 6]. In addition, compared to LMWH, DOACs are (1) less expensive, (2) administered orally, preventing the pain, local hematomas, and allergic reactions related to the subcutaneous LMWH injections, and (3) associated with higher rates of adherence and persistence to treatment [6].

Based on meta-analyses of subgroups of trials limited to active cancer patients, DOACs have proved efficacious and safe to replace traditional oral VKAs for managing recurrent VTE [7, 8]. However, the reduced efficacy of VKAs to prevent recurrent VTEs may be partially related to the lower time in the therapeutic range (i.e., < 70% of the time within the therapeutic range), even in the monitored setting of clinical trials [9]. In addition, it should also be considered that different clinical conditions and scenarios prioritize the use of VKAs over DOACs, such as (1) no availability of DOACs (e.g., low-income countries), (2) empirical implementation by physicians dealing with cancer patients (physician inertia), (3) impaired renal function (4) presence of thrombosis to arterial and venous segments, (5) presence of mechanical valves, (6) antiphospholipid syndrome with an increased number of different antibodies, (7) extreme body weight and (8) previous treatment failure with DOACs [1, 6].

Based on meta-analyses, the benefit of DOACs over LMWH for recurrent VTE yielded conflicting results [10, 11]. Furthermore, this controversy is extended to bleeding event rates, particularly in cancers of the gastrointestinal tract, challenging the safety profile of DOACs [6]. Overall, it remains largely unknown which might be the best alternative to a six-month LMWH anticoagulation treatment for secondary VTE prevention in patients with active cancer.

The net clinical benefit (NCB), an integrated measure of clinical effectiveness, defined as the sum of recurrent VTE and major bleeding events of DOACs vs. LMWH, was not different in a meta-analysis of trials including patients with active cancer [11]. However, the NCB in active cancer patients should be seen more broadly, including beyond the specific benefits and harms of the anticoagulant drug comparison (i.e., VTE recurrence and major bleeding events, respectively), all-cause mortality, and the clinically relevant non-major bleeding events. Therefore, to shed light on these complex problems mentioned above, we conducted a systematic review and meta-analysis of trials or trial subgroups of patients with active cancer. On the same note, the comparison of DOACs vs. usual anticoagulation treatment (i.e., LWMH or VKAs) was examined to estimate the NCB, defined in various ways, as the primary outcome and the individual components of the NCB as secondary outcomes.

Methods

Trial eligibility

Focusing our search on Medline (via PubMed) and Cochrane Collaboration Library, from inception till 8 October 2021, without language restrictions, we tried to detect trials including patients with a history of VTE and active cancer where the comparison between DOACs and LMWH followed or not by VKAs has been examined. Active cancer was defined as any cancer other than non-melanoma skin cancer that (1) was diagnosed in the 6 months before study inclusion, (2) required cancer treatment in the 6 months before randomization, (3) was recurrent or metastatic, (4) was a hematologic malignancy not in complete remission, or (5) was newly diagnosed or recurrent after randomization. The search strategy was mainly organized around, but not limited to, the terms: DOACs, cancer, VTE, deep vein thrombosis, and pulmonary embolism. We also searched the reference list of previous relevant meta-analyses and abstracts presented in major cardiovascular conferences in the last 5 years. Only phase III randomized trials using a therapeutic dose of DOACs compared to a therapeutic dose of LMWH or warfarin were eligible for inclusion. However, we included subgroups of VTE trials in which randomized results for the same drug comparison were available for patients with active cancer at baseline or diagnosed during the individual-trial follow-up period. Trials were also included if randomization occurred on a background of other antithrombotic therapies. We excluded trials with patients (1) without active cancer as previously defined, (2) without a history of VTE, (3) with ages less than 18 years, non-randomized studies, trials comparing different doses of anticoagulant drugs or combination anticoagulant regimens, and phase II trials. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [12]. This review has been registered in PROSPERO (Prospective Register of Systematic Reviews) with identification number CRD42021284238.

Outcomes, data extraction, and risk of bias assessment

The primary outcome of interest [11, 13] was defined arbitrarily as the number of any cause fatal events, recurrent non-fatal VTE, and non-fatal major bleeding events (NCB-1). A

co-primary outcome comprised the NCB-1 and clinically relevant non-major bleeding events (NCB-2). An additional co-primary outcome was the number of fatal and non-fatal recurrent VTE and major bleeding events (NCB-3). The secondary outcomes were as follows: recurrent non-fatal VTE, recurrent fatal and non-fatal VTE, major non-fatal bleedings, fatal and non-fatal major bleedings, clinically relevant non-major bleedings, and all-cause mortality. The definition of outcomes reported in the original articles was retained. However, arterial thromboembolism cases were discarded. Unexplained death was counted as part of all-cause mortality. Recurrent VTE was defined as new upper or lower limb deep vein thrombosis (symptomatic or asymptomatic) or pulmonary embolism at the level of segmental or more proximal pulmonary arteries. Major bleeding and clinically relevant non-major bleeding events were defined according to ISTH (International Society on Thrombosis and Hemostasis) criteria [14]. We extracted individual secondary outcomes as tabulated in the included trials, under the provision that only the first event was counted in patients with more than one event. We separately extracted data for those with active cancer at baseline and follow-up for trials reporting a new active cancer diagnosis during follow-up. Co-primary outcomes were estimated by summing up the individual component outcomes. We also extracted the following clinical characteristics: age, gender, body weight, drug dose, lost-to-follow-up rate, mean follow-up period, and the prevalence of solid cancer at baseline.

Both research and data extraction were independently performed by two authors (H.M. and C.Th.), and any disagreements were resolved by discussion. In case of doubt or missing information, trial authors were consulted. The revised Cochrane Risk of Bias tool (RoB2) was used to assess the quality of all outcomes [15]. It is structured in five mandatory bias domains to address important pathways by which bias may be introduced in each trial outcome result; the overall risk of bias was qualitatively determined by the amount of bias in each risk domain. Whenever at least two domains had some concerns or a high risk of bias, the overall judgment arbitrarily defined the study as biased for our investigation.

Certainty of the evidence

The same two reviewers (H.M. and C.Th.) rated the quality of evidence separately for each co-primary and secondary outcome in the primary population analysis using the grading of recommendations, assessment, development, and evaluation (GRADE) approach [16]. The overall quality rating was made by using different evidence items (i.e., risk of bias, indirectness, inconsistency, imprecision, or other considerations). The quality of evidence grades is defined as "high", "moderate", "low", or "very low". Disagreements between the two review authors over the risk of bias in individual studies and the quality assessment of the evidence were resolved through discussion.

Statistical analysis

All of the analyses were prespecified. In the primary analysis, we considered trials or trial subgroups to compare DOACs and usual anticoagulation treatment of patients diagnosed with active cancer at baseline or follow-up. In contrast, we only considered trials or trial subgroups with active cancer patients at baseline in a secondary analysis. We ran three sensitivity analyses, (1) trials with a low risk of bias, (2) trials with separate outcome data for patients with an on-treatment active cancer diagnosis, and (3) trials where the comparator was LMWH. We also run subgroup analyses to compare trials (1) reporting separate data for active cancer diagnosis at baseline and during follow-up, and (2) in which the comparator was LMWH vs. trials where warfarin was used after a different trial period under LMWH.

Risk ratio estimates with their 95% Confidence Interval (CI) were calculated by the Mantel–Haenszel method using a random-effects model, where the log risk ratio for every trial was weighted according to the reciprocity of the variance. This model was chosen for all the meta-analyses because it avoids assuming that participants in the individual trials are sampled from populations where the intervention has the same quantitative effect. The influence of individual RCTs on pooled effect sizes was tested by excluding one trial at a time (sequential sensitivity analysis). If the point estimate of the combined effect size with a given trial excluded lay outside the CI of the overall estimated risk with all available trials, the trial in question was considered an excessive influence. The proportion of inconsistency across the studies not explained by chance was quantified with the I-squared and the chi-squared Q statistics ($P > 0.1$). In addition, Egger's regression test, Kendall's tau with continuity correction test, and Duval and Tweedie's trim-and-fill test investigated the possibility of publication bias. All statistical analyses were done using the Comprehensive Meta-Analysis version 3.3.070 (Biostat, Englewood, New Jersey, USA). A p-value less than 0.05 indicated statistical significance in each analysis.

Results

Trials and patients

Our searching strategy and the followed investigational procedure to identify the trials to be included are presented in Data Supplement Table S1 and Figure S1, respectively. We identified twelve eligible articles [17–28] reporting

results of four trials [17–20] and four trial subgroups [21–24]. Included studies and clinical characteristics of patients are depicted in Table 1. In four trials, an active cancer diagnosis was available at baseline [17–20]. In contrast, the same diagnosis was made at or after randomization during the on-treatment follow-up period in the trial subgroups [21–24]. In the four trials [17–20], the comparator was LMWH during the entire follow-up period. In the subgroups of trials [21–24], bridging from LMWH to VKAs was attempted after a short period under LMWH or unfractionated heparin. In all trials, the definition of bleeding events was made according to the ISTH criteria [14]. In contrast, in two trials, non-symptomatic limb thrombosis was not considered a deep vein thrombosis case [22, 24]. As shown in Table 1, the average follow-up period was 6 months, while both genders were equally represented across the studies. Less than 10% of cancers were hematological malignancies; among solid cancers, those of the gastrointestinal tract had a variable prevalence ranging from 12 to 44%, while metastatic disease was noticed on average in 45% of all patients. Among the four trials specifically designed to study patients with active cancer [17–20], baseline index events of deep venous thrombosis or pulmonary embolism were reported in 60% of participants. Thus, along with our risk of bias assessment at the study level (Data Supplement, Table S2), five out of eight studies were considered low risk of bias.

Primary outcomes

In our primary analysis, the NCB-1 and -2 were not different between DOACs and usual anticoagulation treatment. In contrast, for the same comparison, the NCB-3 showed a reduction of 28% (95% CI, 10–42%), favoring the treatment with DOACs (Fig. 1). The heterogeneity among trials was low for NCB-1 and -3, at variance with NCB-2, demonstrating a higher heterogeneity. In our secondary analysis, after excluding patients diagnosed with active cancer during follow-up (Data Supplement, Table S3), the summary effect estimates were similar to those of the primary analysis. However, the reduction of the NCB-3 was lower than the primary analysis (21% [95% CI, 3–36%]). Again, the heterogeneity was reduced for all outcomes compared to the primary analysis. We also report the primary outcome estimates, including only patients diagnosed with active cancer during the follow-up (Data Supplement, Table S4). The risk estimates for primary outcomes were different from the primary analysis. In the one study-removed analysis, we did not observe any excessive influence of individual studies on the overall estimate for all primary outcomes in all analyses (data not shown).

Secondary outcomes

In our primary analysis population, the effect of DOACs vs. usual anticoagulation agents (i.e., LMWH or VKAs) on secondary outcomes is reported in Table 2. Recurrent VTE events were, on average, reduced by 40% (95% CI, 25–53%) with DOACs than the usual treatment. Different bleeding outcomes and all-cause mortality were not different between treatment arms. The analysis restricted to patients diagnosed with active cancer only at randomization yielded no different results (Data Supplement, Table S3). In this latter subgroup of patients, no secondary outcome favored DOACs over usual anticoagulation, excluding VTE events. By contrast, VTE events were not reduced when we considered only patients diagnosed with cancer post-randomization (Data Supplement, Table S4). In the one study-removed analysis, we did not observe any excessive influence of individual studies on the overall estimate for all secondary outcomes in all analyses (data not shown).

Sensitivity analyses

Including only the five studies with low-risk bias (Data Supplement, Table S5), co-primary outcomes were not different between groups. At the same time, VTE was lower with DOACs, and clinically relevant non-major bleeding events were lower with usual anticoagulation agents. In sensitivity analysis by different comparators (i.e., LMWH or VKAs), co-primary outcomes were not different between DOACs and LMWH. At the same time, NCB-2 and -3 were reduced with DOACs compared to VKAs (Fig. 2). Component outcomes by comparator drug are reported in Data Supplement, Table S5.

Publication bias

Graphic representations under the random-effects models for the component outcomes of primary and co-primary endpoints deny the presence of significant publication bias. Thus, publication bias cannot change the direction of the observed summary estimates according to the trim-and-fill test. Specific analyses and graphic representations are presented in Data Supplement, Figure S2.

Certainty of the evidence

According to the GRADE approach, the evidence was rated as moderate for NCB-1 and NCB-3, while it was low for NCB-2. In addition, the level of evidence was downgraded from the high level because of the inappropriate

Table 1 Baseline characteristics of the eligible secondary prevention VTE trials in patients with active cancer randomized to DOACs vs. LMWH or warfarin

Trial [references]	Comparison (DOACs dose)	Number	Follow-up, years	Men, %	Age, years mean ± SD	TTR, %	Index event VTE, %	Incidental VTE, %	Previous VTE, %	Metastasis, %	Solid tumor, %	Gastrointestinal tract cancer, %
CARAVAGGIO [17]	Apixaban vs Dalteparin (10 mg twice daily for 7 first days and 5 mg twice daily after that)	576 vs. 579	0.49	49	67 ± 11	–	53	20	9	68	93	32
ADAM VTE [18]	Apixaban vs Daltparin (10 mg twice daily for 7 first days and 5 mg twice daily after that)	150 vs. 150	0.48	49	64 ± 11	–	52	NR	7	62	90	35
Hokusai VTE cancer [19]	Edoxaban vs Dalteparin (60 mg once daily)†, ∫	522 vs. 524	0.59	49	64 ± 11	–	63	33	11	53	89	29
Hokusai VTE [21]	Edoxaban vs. Warfarin (60 mg once daily)†	194 vs. 176*	0.53	57	66 ± 12	63.6	NR	NR	NR	25	92	14
SELECT-D [20]	Rivaroxaban vs Dalteparin (15 mg twice daily for 3 weeks, then 20 mg once daily)	203 vs. 203	0.48	53	67 ± 18	–	72	52	NR	58	93	44
AMPLIFY [22]	Apixaban vs. Warfarin (10 mg twice daily for 7 days followed by 5 mg twice daily)	101 vs. 93*	0.50	58	66 ± 18	57.5	NR	NR	NR	33	NR	> 15
EINSTEIN cancer [23]	Rivaroxaban vs Warfarin or acenocoumarol (15 mg twice daily for 3 weeks, and 20 mg once daily after that)	354 vs. 301*	0.50	56	NR	57.5	NR	NR	NR	23	NR	NR
RECOVER I/II [24]	Dabigatran vs. Warfarin (150 mg twice daily)	173 vs. 162*	0.42	53	64 ± 12	54.5	NR	NR	19	8	91	12

*On-treatment diagnosis of active cancer was made in 85 vs. 77 patients, Hokusai VTE; 88 vs. 71 patients, AMPLIFY; 96 vs. 97, EINSTEIN cancer; and 59 vs. 55, RECOVER I/II

†It was administered at a lower dose (30 mg once daily) in patients with a creatinine clearance of 30 to 50 ml per minute, a body weight of 60 kg or less, or in those receiving concomitant treatment with potent P-glycoprotein inhibitors

∫Edoxaban was started after a course of therapeutic-dose low-molecular-weight heparin or unfractionated heparin for at least 5 days

DOACs direct oral anticoagulants, *LMWH* low-molecular-weight heparin, *NR* not reported, *VTE* venous thromboembolism

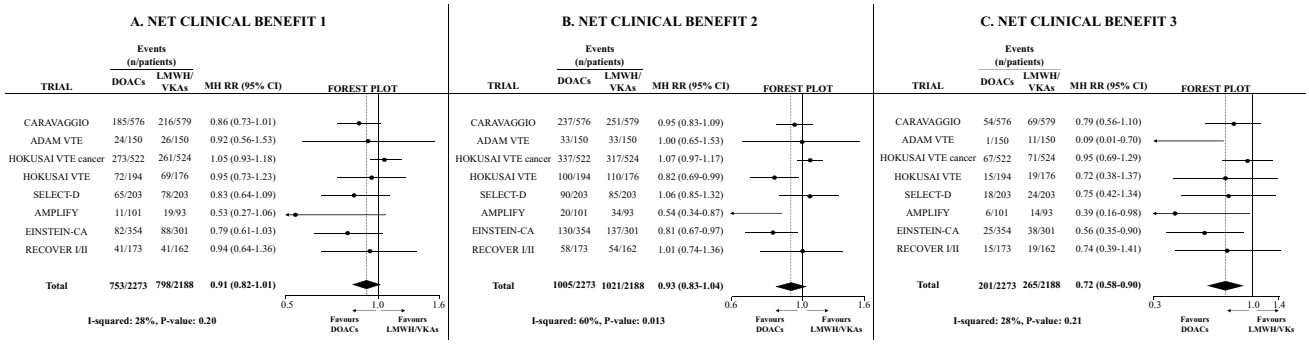


Fig. 1 Net clinical benefit of DOACs vs. standard anticoagulation treatment for the secondary prevention of venous thromboembolism in patients with active cancer. Panel **A**, net clinical benefit 1 (i.e., any cause of fatal events, recurrent non-fatal venous thromboembolism, and non-fatal major bleeding events); Panel **B**, net clinical benefit 2 (i.e., any cause of fatal events, recurrent non-fatal venous thromboembolism, and non-fatal major or clinically relevant non-major bleeding events); Panel **C**, net clinical benefit 3 (i.e., fatal and non-fatal recurrent venous thromboembolism and major bleeding events). For study acronyms, refer to the abbreviation list. Within each forest plot, filled circles and lines represent the mean effect estimate and confidence interval in each trial, respectively, while rectangles represent the summary effect estimate defined by the dotted vertical fine line and respective confidence interval. CI, confidence interval; DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin; MH RR, Mantel–Haenszel risk ratio; n, number; VKAs, vitamin K antagonists

Table 2 Secondary outcomes in secondary prevention VTE trials in patients* with active cancer randomized to DOACs vs LMWH or warfarin

Outcome	Trials or subgroups of trials, n	Events/n = 2273, DOACs group	Events/n = 2188, Warfarin group	RR (95% CI) Random-effects	I-squared, P-value
Non-fatal VTE	8	104	176	0.59 (0.46–0.75)	0%, 0.54
Fatal/non-fatal VTE	8	109	182	0.60 (0.47–0.75)	0%, 0.55
Non-fatal major bleedings	8	91	74	1.11 (0.70–1.76)	45%, 0.074
Fatal/non-fatal major bleedings	8	91	84	0.99 (0.66–1.47)	35%, 0.15
Clinically relevant non-major bleedings	8	252	223	1.09 (0.78–1.51)	68%, 0.003
All-cause mortality	8	558	548	1.00 (0.90–1.10)	0%, 0.61

*Patients with active cancer diagnosed during follow-up were also included

CI confidence interval, *DOACs* direct oral anticoagulants, *LMWH* low-molecular weight heparin, *n* number, *RR* Mantel–Haenszel risk ratios, *VTE* venous thromboembolism

blinding of participants and personnel or inconsistency for some component outcomes (Data Supplement, Table S6).

Discussion

The NCB of DOACs was similar or more favorable to usual anticoagulation strategies in patients with active cancer due to a substantial reduction of VTE events and no bleeding excess. Therefore, DOACs should be considered for the prevention of recurrent VTE in patients with active cancer unless a contraindication to oral administration emerges, like a gastrointestinal malignancy, problems of intake or absorption, drug interactions of DOACs with chemotherapeutic agents, or finally, in patients with severe renal impairment.

Our analysis has unique features compared to previous meta-analyses in the field. First, we used NCB as the primary outcome because, in patients with active cancer, the balance between thrombosis prevention and bleeding events is fragile, making the *pros* and *cons* of any eligible treatment largely unpredictable. Second, we did not examine only outcomes of the same clinical importance following anticoagulation treatment, namely VTE and major bleeding events. Nevertheless, we have also considered all-cause mortality and clinically relevant non-major bleedings. Indeed, patients with active cancer are mostly critically ill; therefore, a given treatment should not impact survival and avoid complications jeopardizing vital organ homeostasis, like those deriving from minor bleedings. Third, we refrained from using LMWH as the only comparator of DOACs. In the usual clinical practice, patients with active cancer receive an oral anticoagulation agent to minimize patient discomfort from daily injections and economic costs for the patient and the health system. Moreover, it is unknown whether the benefits

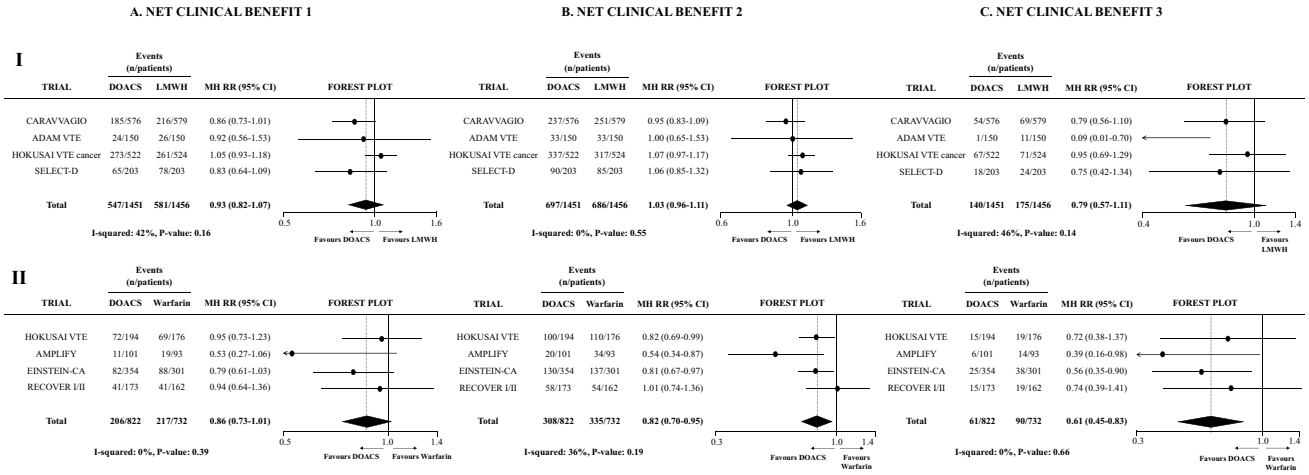


Fig. 2 Comparator-related sensitivity analyses for net clinical benefit effect of DOACs vs. comparator (i.e., LMWH or VKAs) for the secondary prevention of venous thromboembolism in patients with active cancer. Panel **A**, net clinical benefit 1 (i.e., any cause of fatal events, recurrent non-fatal venous thromboembolism, and non-fatal major bleeding events); Panel **B**, net clinical benefit 2 (i.e., any cause of fatal events, recurrent non-fatal venous thromboembolism, and non-fatal major or clinically relevant non-major bleeding events); Panel **C**, net clinical benefit 3 (i.e., fatal and non-fatal recurrent venous thromboembolism and major bleeding events). Comparison between DOACs and LMWH (upper part, I) or vitamin K antagonists (lower part, II). For study acronyms, refer to the abbreviation list. *CI* confidence interval, *DOACS* direct oral anticoagulants, *LMWH* low molecular weight heparin, *MH-RR* Mantel–Haenszel risk ratios, *n* number

of LMWH are extended to periods beyond six months from the active cancer diagnosis. However, there is evidence that VTE recurrence remains common beyond six months, and the continuation of different anticoagulation strategies, even with a reduced dose of DOACs, has an acceptable safety profile [29, 30]. Fourth, our analysis included patients diagnosed with active cancer during follow-up recruited in trials designed not to study the recurrent VTE in cancer specifically. Therefore, our meta-analysis used an increased number of patients with active cancer. Finally, our sensitivity analyses demonstrated that DOACs (1) reduce the more restricted NCB outcome compared either to LMWH or VKAs, (2) reduce the most expanded NCB outcome compared to VKAs, and (3) have no differential effect on co-primary outcomes in trials of low risk of bias, (4) are characterized by the same risk/benefit ratio compared with LMWH, since they protect better for VTE, but at the cost of a more increased clinically relevant non-major bleeding burden, and (5) have a more favorable NCB profile compared to VKAs as the result of a better VTE protection with no differential effect on bleeding events.

In the meta-analysis by Mulder et al. [11], the estimated NCB was the composite of fatal and non-fatal VTE and major bleeding events, thus resembling our NCB-3. Only trials using LMWH as a comparator were used [17–20], while the comparison of DOACs vs. VKAs was discarded. Other differences compared to the present report are the following: (1) they considered unexplained deaths in one trial [17] as deaths related to pulmonary embolism, (2) they conducted their primary analysis including only the three trials with baseline symptomatic VTE [17, 19, 20], and thus one out of four trials [18] was excluded because of inclusion of patients with incidental VTE, and (3) unpublished data from three trials [18–20] were used to homogenize the results not available in our case. Our analysis cannot be compared with the direct comparison between DOACs and LMWH by Rossel et al. [10] because only two trials were used [22, 23]. By contrast, recurrent VTE and major bleeding estimates reported by Haykal et al. [31] for comparing DOACs and LMWH were not substantially different from our relevant sensitivity analysis. Although no difference in pooled estimates was detected for benefits and harms between RCTs and observational studies in the analysis by Gu et al. [32], our study estimates did not differ for the same outcomes in a larger number of RCTs available in our analysis.

Different limitations are acknowledged. First, different DOACs were used, and the generalization to all DOACs can only be extrapolated. However, no study significantly impacted the summary estimate for all outcomes in a sensitivity analysis of a sequential exclusion of one study each time. Second, composite outcomes like the NCB may introduce bias and should be interpreted with caution because composite outcomes (1) may not have the same clinical importance, (2) may have different incident rates making the composite outcome clinically unbalanced, and (3) may integrate different component relative risk changes, making the overall combined effect estimate a "by-chance" finding. Third, we acknowledge that the time

in the therapeutic ratio was suboptimal in VKAs trials, ranging from 54 to 64%. However, this phenomenon is not different from the inadequate anticoagulation control observed in the usual clinical practice, modifying the risk of ischemic and hemorrhagic outcomes compared to 70% or above the optimal target [33]. Fourth, although statistical heterogeneity was low to moderate for most outcomes, it was reduced in sensitivity analyses of most homogeneous populations, suggesting that the studied populations across studies had at least different clinical characteristics. Fifth, trials comparing DOACs to warfarin post-hoc subset data were used, and several types of bias were potentially introduced at variance with trials comparing DOACs to LMWH. Sixth, the quality of our risk estimates according to GRADE was low to moderate because of bias for the blinding procedure in the risk of bias assessment and the notable heterogeneity between studies for some outcomes. We finally acknowledge the following issues. The time and dosing of the LMWH and DOACs co-administration in different studies may introduce bias of inequal comparison compared to traditional anticoagulation treatments, and not all studies share a similar treatment protocol for different DOACs.

Conclusion

LMWH, having been considered for years as the pivotal treatment in the context of cancer-associated VTE, an entity governed by the unstable equilibrium due to the frequently recurrent thromboembolic and bleeding risk, are now getting a strong rival that offers several competitive advantages. In comparing DOACs with other anticoagulant strategies to prevent recurrent VTE in patients with active cancer, the balance between benefits and harms favors DOACs. However, anticoagulant treatment should be individualized in patients with active cancer, and LMWH agents may occasionally be preferred over DOACs. Although VKAs proved less beneficial in terms of an NCB than DOACs, their use may be reserved for special clinical indications or whenever the use of DOACs or LMWH is limited, mostly because of socio-economical barriers, especially in low-income countries. Future trials may compare the efficacy and safety of DOACs in specific cancer settings, while future guidelines may consider economic issues for drafting updated recommendations.

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Declarations

Conflict of interest All authors declare no conflict of interest regarding the present work, and they have no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

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