ONLINE **EXCLUSIVE**

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Q/ What's the best VTE treatment for patients with cancer?

EVIDENCE-BASED ANSWER

A/ NO HEAD-TO-HEAD STUDIES DI-RECTLY COMPARE all the main treatments for venous thromboembolism (VTE) in cancer patients. Long-term treatment (3-12 months) with low-molecular-weight heparin (LMWH) reduces recurrence of VTE by 40% compared with vitamin K antagonists (VKA), but doesn't change rates of mortality, major or minor bleeding, or intracranial hemorrhage in patients with solid or hematologic cancer at any stage or in any age group. Initial treatment with LMWH reduces mortality by 30% compared with unfractionated heparin (UFH) for 5 to 10 days followed by warfarin, but doesn't alter recurrent VTE or bleeding. Non-vitamin K oral anticoagulants (NOACs) have risks of recurrent VTE or VTE-related death (composite outcome) and clinically significant bleeding comparable to VKA or LMWH/VKA (strength of recommendation [SOR]: **B**, meta-analyses of randomized controlled trials [RCTs], mostly of low quality).

Evidence summary

No head-to-head studies or umbrella meta-analyses assess all the main treatments for VTE against each other.

Long-term LMWH decreases VTE recurrence compared with VKA

Two meta-analyses of RCTs evaluating LMWH and VKA for long-term treatment (3-12 months) of confirmed VTE in patients with cancer found that LMWH didn't change mortality, but reduced the rate of VTE recurrence compared with VKA (40% relative reduction).[1,2] The comparison showed no differences in major or minor bleeding or thrombocytopenia between LMWH and VKA (**TABLE**[1-5]).

The studies included patients with any solid or hematologic cancer at any stage and from any age group, including children. Overall, the mean age of patients was in the mid 60s; approximately 50% were male when specified. Investigators rated the evidence quality as moderate for VTE, but low for the other outcomes.[1]

The most recent meta-analysis of the same RCTs comparing LMWH with VKA evaluated intracranial hemorrhage rates and found no difference.[3]

Initial therapy with LMWH: A look at mortality

A meta-analysis of RCTs that compared LMWH with UFH/VKA for initial treatment of confirmed VTE in adult cancer patients (any type or stage of cancer, mean ages not specified) found that LMWH reduced mortality by 30%, but didn't affect VTE recurrence or major bleeding.[4]

The control groups received UFH for 5 to 10 days and then continued with VKA, whereas the experimental groups received different types of LMWH (reviparin, nadroparin, tinzaparin, enoxaparin) initially and for 3 months thereafter. Investigators rated all studies low quality because of imprecision and publication bias favoring LMWH.

Fondaparinux shows no advantage for initial therapy

The same meta-analysis compared initial treatment with fondaparinux and initial therapy with enoxaparin or UFH transitioning to

TABLE
How VTE treatments for patients with active cancer* compare

Comparison	Number of RCTs in meta-analysis (number of patients)	Outcomes	Risk ratio (95% CI)
LMWH vs VKA, long-term	7 (1009)[1]	Survival, 3-6 mo	0.96 (0.81-1.14)
	6 (2078)[2]	Recurrent VTE	0.60 (0.45-0.79)[†]
	6 (2020)[2]	Major bleeding	1.07 (0.66-1.73)
	4 (1091)[1]	Minor bleeding	0.89 (0.51-1.55)
	2 (341)[1]	Thrombocytopenia	0.98 (0.57-1.66)
	5 (2089)[3]	Intracranial hemorrhage	0.49 (0.10-2.33)
LMWH vs UFH/VKA, initial	11 (801)[4]	Mortality at 3 mo	0.71 (0.52-0.98)[†]
	3 (371)[4]	Recurrent VTE	0.78 (0.29-2.08)
Fondaparinux vs UFH or LMWH	2 (477)[4]	Mortality at 3 mo	1.27 (0.88-1.84)
		Recurrent VTE	0.95 (0.57-1.6)
NOAC vs VKA	4 (1164)[2]	Recurrent VTE	0.65 (0.38-1.09)
	4 (1145)[2]	Major bleeding	0.72 (0.39-1.37)
NOAC vs LMWH/VKA	6 (1075)[5]	Recurrent VTE	0.80 (0.39-1.65)
		Clinically relevant bleeding	1.49 (0.82-2.71)

*Solid or hematologic cancer at any stage and in any age group.

†Statistically significant.

CI, confidence interval; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K oral anticoagulant; RCT, randomized controlled trial; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

warfarin.[4] It found no differences in any outcomes at 3 months. Investigators rated both studies as low quality for recurrent VTE and moderate for mortality and bleeding.

Non-vitamin K oral anticoagulants vs LMWH/VKA or VKA: No differences
A meta-analysis of RCTs comparing NOACs (dabigatran, edoxaban, apixaban, rivaroxaban) with VKA for 6 months found no differences in recurrent VTE or major bleeding.[2]

A second meta-analysis of RCTs that compared NOACs (rivaroxaban, dabigatran, apixaban) with control (LMWH followed by VKA) in adult cancer patients (mean ages, 54-66 years; 50%-60% men) reported no difference in the composite outcome of recurrent VTE or VTE-related death nor clinically significant bleeding over 1 to 36 months (most RCTs ran 3-12 months).[5] Separate comparisons for rivaroxaban and dabigatran found no difference in the composite outcome, and rivaroxaban also produced no difference in clinically-significant bleeding.

Recommendations
The 2016 CHEST guidelines recommend LMWH as first-line treatment for VTE in patients with cancer and indicate no preference between NOACs and VKA for second-line treatment.[6] **JFP**

References
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