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Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer
A Randomized Clinical Trial

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IMPORTANCE Low-molecular-weight heparin is recommended over warfarin for the treatment of acute venous thromboembolism (VTE) in patients with active cancer largely based on results of a single, large trial.

OBJECTIVE To study the efficacy and safety of tinzaparin vs warfarin for treatment of acute, symptomatic VTE in patients with active cancer.

DESIGN, SETTINGS, AND PARTICIPANTS A randomized, open-label study with blinded central adjudication of study outcomes enrolled patients in 164 centers in Asia, Africa, Europe, and North, Central, and South America between August 2010 and November 2013. Adult patients with active cancer (defined as histologic diagnosis of cancer and receiving anticancer therapy or diagnosed with, or received such therapy, within the previous 6 months) and objectively documented proximal deep vein thrombosis (DVT) or pulmonary embolism, with a life expectancy greater than 6 months and without contraindications for anticoagulation, were followed up for 180 days and for 30 days after the last study medication dose for collection of safety data.

INTERVENTIONS Tinzaparin (175 IU/kg) once daily for 6 months vs conventional therapy with tinzaparin (175 IU/kg) once daily for 5 to 10 days followed by warfarin at a dose adjusted to maintain the international normalized ratio within the therapeutic range (2.0-3.0) for 6 months.

MAIN OUTCOMES AND MEASURES Primary efficacy outcome was a composite of centrally adjudicated recurrent DVT, fatal or nonfatal pulmonary embolism, and incidental VTE. Safety outcomes included major bleeding, clinically relevant nonmajor bleeding, and overall mortality.

RESULTS Nine hundred patients were randomized and included in intention-to-treat efficacy and safety analyses. Recurrent VTE occurred in 31 of 449 patients treated with tinzaparin and 45 of 451 patients treated with warfarin (6-month cumulative incidence, 7.2% for tinzaparin vs 10.5% for warfarin; hazard ratio [HR], 0.65 [95% CI, 0.41-1.03]; $P = .07$). There were no differences in major bleeding (12 patients for tinzaparin vs 11 patients for warfarin; HR, 0.89 [95% CI, 0.40-1.99]; $P = .77$) or overall mortality (150 patients for tinzaparin vs 138 patients for warfarin; HR, 1.08 [95% CI, 0.85-1.36]; $P = .54$). A significant reduction in clinically relevant nonmajor bleeding was observed with tinzaparin (49 of 449 patients for tinzaparin vs 69 of 451 patients for warfarin; HR, 0.58 [95% CI, 0.40-0.84]; $P = .004$).

CONCLUSIONS AND RELEVANCE Among patients with active cancer and acute symptomatic VTE, the use of full-dose tinzaparin (175 IU/kg) daily compared with warfarin for 6 months did not significantly reduce the composite measure of recurrent VTE and was not associated with reductions in overall mortality or major bleeding, but was associated with a lower rate of clinically relevant nonmajor bleeding. Further studies are needed to assess whether the efficacy outcomes would be different in patients at higher risk of recurrent VTE.

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Group Information: CATCH Investigators are listed at the end of this article.

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in patients with cancer.[1,2] Treatment with low-molecular-weight heparin (LMWH) is effective and is recommended over vitamin K antagonist therapy by clinical practice guidelines.[3-6] These recommendations are largely based on results from a single, large randomized trial with supportive evidence from additional smaller studies that were conducted over a decade ago in academic centers primarily in North America and Western Europe.[7-10] These limitations may partly explain why vitamin K antagonists remain frequently used worldwide in patients with cancer-associated thrombosis.[11,12] To provide more contemporary and global evidence for long-term LMWH therapy, we conducted the Comparison of Acute Treatments in Cancer Hemostasis (CATCH) trial to compare the efficacy and safety of tinzaparin with conventional warfarin therapy for the treatment of VTE in patients with active cancer.

DVT *deep vein thrombosis*

HIT *heparin-induced thrombocytopenia*

INR *international normalized ratio*

LMWH *low-molecular-weight heparin*

TTR *time in the INR therapeutic range*

VTE *venous thromboembolism*

Methods

Study Design and Oversight

This phase 3, multinational, randomized, active-controlled, open-label trial was designed, conducted, and supervised by a steering committee of academic physicians and sponsor representatives. Members of a central, independent adjudication committee, who were unaware of the study treatment assignments, reviewed and adjudicated all suspected cases of recurrent VTE, heparin-induced thrombocytopenia (HIT), bleeding events, and causes of death. An independent data and safety monitoring committee regularly received data on study outcomes and adverse events. Institutional ethics approval was obtained at each participating center and written informed consent was obtained from each participant. The trial was designed in accordance with the International Conference on Harmonisation Guidelines of Good Clinical Practice and the Declaration of Helsinki (trial protocol in Supplement 1).

Details and rationale of study methods were published previously and are briefly described here.[13]

Study Population

Patients 18 years or older with a diagnosis of active cancer and acute symptomatic proximal deep vein thrombosis (DVT), pulmonary embolism, or both were eligible for inclusion (**Figure 1**). Active cancer was defined by histological or cytological confirmation of malignancy (excluding basal cell carcinoma or nonmelanoma skin cancer) and having any of the following features: cancer diagnosis within the previous 6 months; recurrent, regionally advanced, or metastatic disease; treatment for cancer during the previous 6 months; or not in complete remission from a hematological malignancy. Proximal DVT was defined as thrombosis involving the popliteal, femoral, or iliac veins. Objective confirmation of DVT and pulmonary embolism using standard imaging techniques and diagnostic criteria was required.[13] Patients also had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 prior to the index thrombotic event (ie, their activity level ranged from no limitation [score 0] to being unable to work but able to perform self-care and remain ambulatory for at least 50% of waking hours [score 2]).

Patients were excluded for any of the following: creatinine clearance of 20 mL/min/1.73 m^2 or lower (to convert creatinine clearance to mL/s/m^2, multiply by 0.0167); any contraindication to anticoagulation; known hypersensitivity to study medications; history of HIT; therapeutic anticoagulation for more than 72 hours prior to randomization; therapeutic anticoagulation at the time of thrombotic event; life expectancy less than 6 months; unlikely to comply with the protocol; participating in another interventional study; women of childbearing potential or fertile men not using effective contraception.

Randomization and Concealment

Randomization occurred within the first 72 hours after confirmation of the qualifying thrombotic event or initiation of therapeutic anticoagulation. Prior to randomization, all patients had diagnostic imaging for both DVT and pulmonary embolism to document any additional VTE at baseline. Treatment assignment was preplanned according to a computer-generated randomization schedule in a 1:1 ratio and concealed until individual randomization using an interactive voice-response system. Randomization was stratified by tumor extent (known distant metastasis, no distant metastasis, or hematological malignancy); geographic region (Asia and Middle East; Eastern Europe; Western Europe and North America; and Central and South America); and history of VTE.

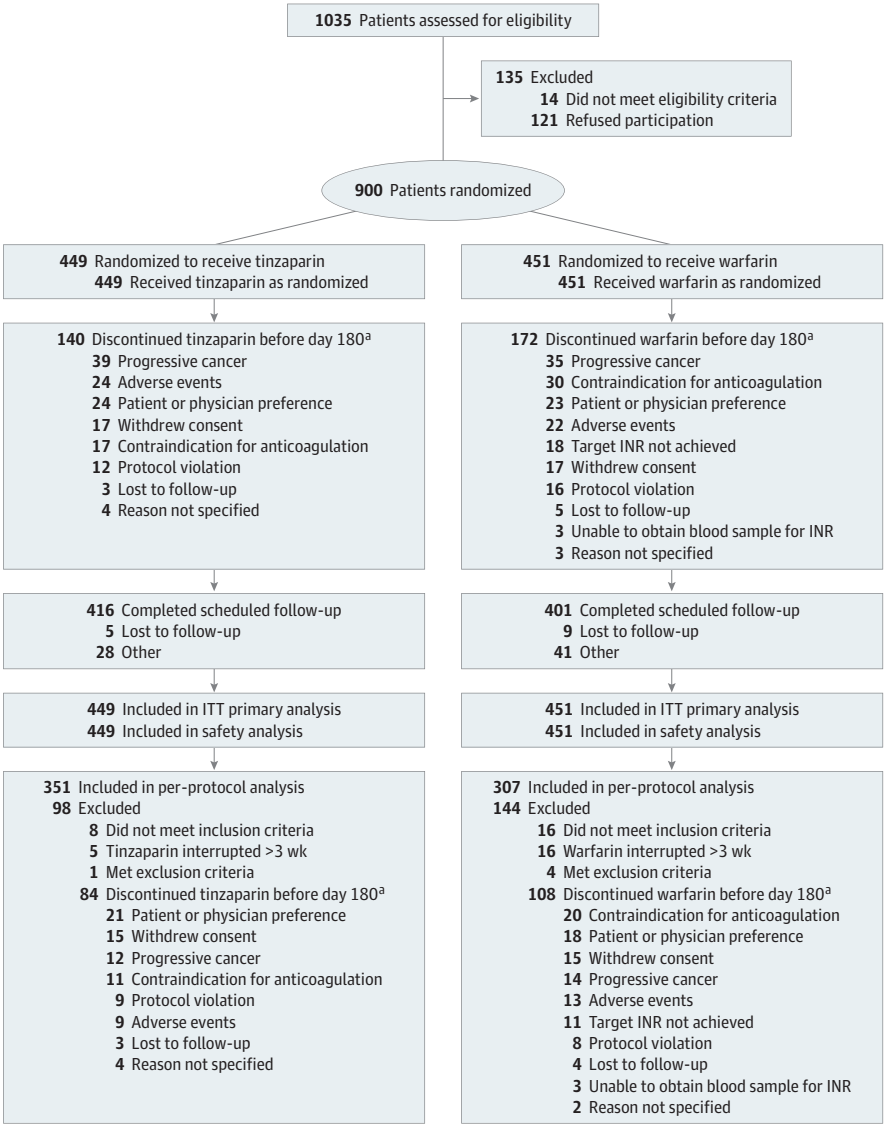
Study Treatments

Patients in the tinzaparin (Innohep, LEO Pharma A/S) group received tinzaparin (175 IU/kg) once daily by subcutaneous injection for 6 months. Patients in the warfarin group received warfarin for 6 months, overlapping with tinzaparin (175 IU/kg) once daily for the first 5 to 10 days and until the international normalized ratio (INR) was higher than 2.0 for 2 consecutive days. Thereafter, these patients continued on warfarin alone at a dose adjusted to maintain the INR within the therapeutic range (2.0-3.0). INR testing was required at least once every 2 weeks. Temporary interruption of the study drug not exceeding 3 weeks was permitted for a platelet count lower than 50 × 10^3/μL, a bleeding event, or invasive procedures.

Efficacy Outcomes

The primary efficacy outcome was the composite of symptomatic DVT, symptomatic nonfatal pulmonary embolism, fatal pulmonary embolism, incidental proximal DVT

Figure 1. Patient Screening, Enrollment, Follow-up, and Analysis of the CATCH Trial



INR indicates international normalized ratio; ITT, intention-to-treat.

[a] Study drug was stopped for reasons other than death or a thrombotic event.

(popliteal vein or anatomically more proximal), and incidental proximal pulmonary embolism (segmental arteries or larger). Each component was a secondary efficacy outcome.

Incidental VTE was defined as DVT or pulmonary embolism detected during imaging performed for other reasons (eg, cancer staging).[14]

Recurrent DVT and nonfatal pulmonary embolism were objectively confirmed using standard imaging techniques, including venous ultrasonography, contrast venography, computer tomography venography, or magnetic resonance venography for DVT; and ventilation-perfusion scintigraphy, standard pulmonary angiography, or computer tomography angiography for pulmonary embolism. Fatal pulmonary embolism was defined as proven on objective imaging, autopsy, or as the most probable cause of a sudden and unexplained death according to central adjudication. Only events diagnosed between randomization and the day 180 visit that were validated by central adjudication were included in the efficacy analyses.

Safety Outcomes

Principal safety outcomes were major bleeding, clinically relevant nonmajor bleeding, and all-cause mortality. Major bleeding events included those that were fatal; occurred in a critical area or organ (eg, intracranial); or caused a fall in hemoglobin of 2 g/dL or more or led to a transfusion of 2 or more units of whole blood or red cells.[15] All nonmajor bleeding events that required any medical or surgical intervention were classified as clinically relevant nonmajor bleeding. Only those bleeding events that occurred within 24 hours after the last dose of study drug and confirmed by adjudication were included in the bleeding outcome analyses.

In addition, cases of suspected HIT were centrally adjudicated based on the Warkentin 4T score and laboratory confirmation.

All deaths were adjudicated centrally and a cause of death was assigned as due to pulmonary embolism, bleeding, cancer progression, or other known conditions.

Study Follow-up

Follow-up visits occurred on days 7, 14, 30, and then every 30 days until day 180. Telephone contacts were made 2 weeks after the monthly visits. Each scheduled visit and telephone contact included a standardized assessment of the signs and symptoms of recurrent thrombosis and bleeding and a reminder to patients to notify the research staff if they developed signs and symptoms between scheduled assessments. Appropriate objective testing was performed in patients with symptoms to confirm or exclude VTE. If recurrent VTE was confirmed, end-of-treatment assessments were conducted and therapy for recurrent thrombosis was initiated according to local practice.

All patients were followed for the primary composite efficacy outcome and for all-cause mortality up to day 180 or death, whichever occurred first. Patients were followed up for safety outcomes and serious adverse events until 1 month following the last dose of study treatment.

Statistical Analyses

The trial was designed to demonstrate superiority of tinzaparin over warfarin in reducing the risk of recurrent VTE. Based on published data, we estimated a 6-month cumulative event rate of 12.6% in the warfarin group (statistical analysis in Supplement 2).[7-10] Assuming a relative risk reduction of 50% with tinzaparin and using a time-to-event analysis with a 2-sided significance level of $P = .05$ and an overall power of 90%, a sample size of 847 patients was required. Incorporating an expected dropout rate of 5%, the target sample size was 900 patients. A prespecified sample size reestimation was conducted on blinded composite data when approximately 25% of patients had completed the treatment period, died, or been lost to follow-up. This analysis supported maintaining the original sample size.

The efficacy population included all randomized patients. Comparisons between groups were based on time to first recurrent VTE and accounted for deaths not due to fatal pulmonary embolism as a competing risk. The cumulative incidence functions and the corresponding 95% CIs were estimated in a competing risk regression model[16] and the cumulative incidence functions were compared between the 2 treatment groups using a Wald test. For each time-to-event analysis, the components not defined as the event of interest were considered a competing risk. A per-protocol efficacy analysis was also prespecified, which excluded patients if they had a major protocol violation (eg, did not have eligible VTE or active cancer) or discontinued the study drug prior to day 180 for more than 3 consecutive weeks or for any other reason except for death or having a recurrent thrombotic event.

The safety population included all patients who received at least 1 dose of study drug. Similar to efficacy analyses, competing risk time-to-event analysis was performed for first major bleeding event and for first clinically relevant nonmajor bleeding.

Overall mortality was summarized with Kaplan-Meier estimates and compared between treatment groups using a stratified log-rank test.

The significance threshold for secondary analyses was not adjusted for multiple comparisons. All analyses were conducted using SAS (SAS Institute), version 9.3, and Stata (StataCorp), version 13.1.

Results

Patient Enrollment and Baseline Characteristics

From August 2010 to November 2013, 1035 patients were screened and 900 patients were enrolled from 164 centers in 32 countries; 449 were randomized to receive tinzaparin and 451 to receive warfarin (Figure 1 and **Table 1**). The median number of patients enrolled per site was 4 (range, 1-38; interquartile range, 2-7). Of these, 23 patients did not have a qualifying episode of thrombosis (eg, incidental or distal thrombosis) and 1 patient did not have histological confirmation of cancer. These 24 patients received study treatment and were followed up according to protocol. All 900 patients received assigned study treatment and 817 patients (91%) completed scheduled follow-up.

The demographic data, clinical status, and medical history of the patients were well balanced at baseline between the 2 treatment groups and within each stratum (Table 1). Overall, 89.6% of the patients had solid tumors (54.7% had metastatic disease) and 10.4% had hematological malignancy; 52.9% were receiving anticancer therapy and 6.3% of the patients had previous VTE. The qualifying symptomatic thrombotic event was DVT in 683 patients (75.9%) and pulmonary embolism with or without DVT in 194 patients (21.6%). Additional thrombosis was found with baseline testing in 194 patients (21.6%). The most common primary tumor sites were gynecologic, colorectal, upper gastrointestinal, and lung.

Anticoagulant Treatment

The study treatment duration was longer in the tinzaparin group (median, 168 days [range, 1-216]) than in the warfarin group (median, 127 days [range, 1-209]). Study treatment was interrupted for a median of 5 days (range, 2-40) in 21% of patients. Of these, 10 discontinued study drug permanently after an interruption lasting longer than 3 weeks. In patients treated with warfarin, the mean time in the INR therapeutic range (TTR) was 47.0%.[17] The percentage of time below the therapeutic range was 26.1% and time above was 26.9%. In patients treated with tinzaparin, 86% received an injection for at least 75% of the treatment days.

Efficacy Outcomes

Recurrent VTE occurred in 31 patients in the tinzaparin group and 45 patients in the warfarin group (cumulative

risks, 7.2% for the tinzaparin group vs 10.5% for the warfarin group; hazard ratio [HR], 0.65 [95% CI, 0.41-1.03]; *P* = .07; **Figure 2**, left panel). Symptomatic DVT occurred in 12 patients in the tinzaparin group and in 24 patients in the warfarin group. Symptomatic nonfatal pulmonary embolism occurred in 3 patients in the tinzaparin group and 2 patients in the warfarin group and fatal pulmonary embolism occurred in 17 patients in each group. Incidental VTE occurred in 2 patients; both were in the warfarin group. **Table 2** summarizes the results of the efficacy outcomes.

Safety Outcomes

Major bleeding events occurred in 12 patients assigned to tinzaparin and 11 patients assigned to warfarin (HR, 0.89 [95% CI, 0.40-1.99]; *P* = .77; Figure 2, right panel, and Table 2). Clinically relevant nonmajor bleeding occurred in 49 patients in the tinzaparin group compared with 69 patients in the warfarin group (HR, 0.58 [95% CI, 0.40-0.84]; *P* = .004).

There were no confirmed cases of HIT.

Death occurred in 150 patients in the tinzaparin group and 138 patients in the warfarin group (cumulative risk, 34.7% for the tinzaparin group vs 32.2% for the warfarin group; HR, 1.08 [95% CI, 0.85-1.36]; *P* = .54; **Figure 3**). No differences in cause of death were observed between the treatment groups. Progression of cancer was the most frequent cause of death (69%), followed by other known causes (16.4%), fatal pulmonary embolism (12.5%), and bleeding (2.1%). All cases of fatal pulmonary embolism were deaths adjudicated by central adjudication; none except 1 case had objective imaging or autopsy confirmation.

Additional Adverse Events

Adverse events led to study drug discontinuation in 5.3% of patients assigned to the tinzaparin group and in 5.1% of patients assigned to the warfarin group. Serious adverse events occurred in 49.2% of the tinzaparin group and 43.2% of the warfarin group, with progression of disease as the most common reason.

Per-Protocol Efficacy Analysis

A total of 658 patients (tinzaparin, 351; warfarin, 307) were included in the per-protocol analysis (Figure 1). The cumulative incidence of recurrent VTE in the per-protocol set was 8.3% in the tinzaparin group compared with 12.7% in the warfarin group (HR, 0.62 [95% CI, 0.38-1.00]; *P* = .05).

Discussion

To our knowledge, CATCH is the largest trial to study the efficacy and safety of LMWH relative to warfarin for the treatment of acute VTE in patients with active cancer. Tinzaparin did not significantly reduce the composite primary outcome of recurrent VTE and was not associated with reductions in overall mortality or major bleeding, but reduced the risk of clinically relevant nonmajor bleeding.

Table 1. Baseline Characteristics of Patients in the CATCH Trial

	No. (%)	
	Tinzaparin (n = 449)	Warfarin (n = 451)
Age, mean (SD), y	59.7 (12.7)	58.8 (12.5)
Sex		
Women	262 (58.4)	273 (60.5)
Men	187 (41.6)	178 (39.5)
Location		
Asia and Middle East	196 (43.7)	195 (43.2)
Eastern Europe	94 (20.9)	96 (21.3)
Western Europe and North America	75 (16.7)	75 (16.6)
Central and South America	84 (18.7)	85 (18.8)
Weight, mean (SD), kg	67.3 (17.3)	67.1 (16.3)
Creatinine clearance, mL/min/1.73 m^2		
<30	8 (1.8)	2 (0.4)
30-<60	59 (13.1)	60 (13.3)
≥60	355 (79.1)	378 (83.8)
Noncalculable due to missing data	27 (6.0)	11 (2.4)
Primary tumor site		
Gynecologic	101 (22.5)	102 (22.6)
Colorectal	66 (14.7)	53 (11.8)
Upper gastrointestinal	56 (12.5)	49 (10.9)
Lung	48 (10.7)	56 (12.4)
Genitourinary	53 (11.8)	41 (9.1)
Hematologic	44 (9.8)	50 (11.1)
Breast	37 (8.2)	47 (10.4)
Other	44 (9.8)	53 (11.8)
Known metastases	247 (55.0)	245 (54.3)
Cancer therapy[a]	228 (50.8)	248 (55.0)
Systemic medical therapy[b]	189 (42.1)	193 (42.8)
Radiation	51 (11.4)	41 (9.1)
Surgery	24 (5.3)	38 (8.4)
Hospitalization 3 d or longer[c]	140 (31.2)	146 (32.4)
Immobility[c]	33 (7.3)	45 (10.0)
ECOG performance status		
0 or 1	343 (76.4)	348 (77.2)
2	106 (23.6)	103 (22.8)
Previous history of VTE	27 (6.0)	30 (6.7)
Qualifying thrombotic event		
Symptomatic DVT	252 (56.1)	259 (57.4)
Symptomatic DVT with incidental PE	82 (18.3)	90 (20.0)
Symptomatic PE	48 (10.7)	44 (9.8)
Symptomatic PE with incidental DVT	11 (2.4)	11 (2.4)
Symptomatic PE and symptomatic DVT	48 (10.7)	32 (7.1)
No qualifying VTE	8 (1.8)	15 (3.3)

Abbreviations: DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; PE, pulmonary embolism; VTE, venous thromboembolism.

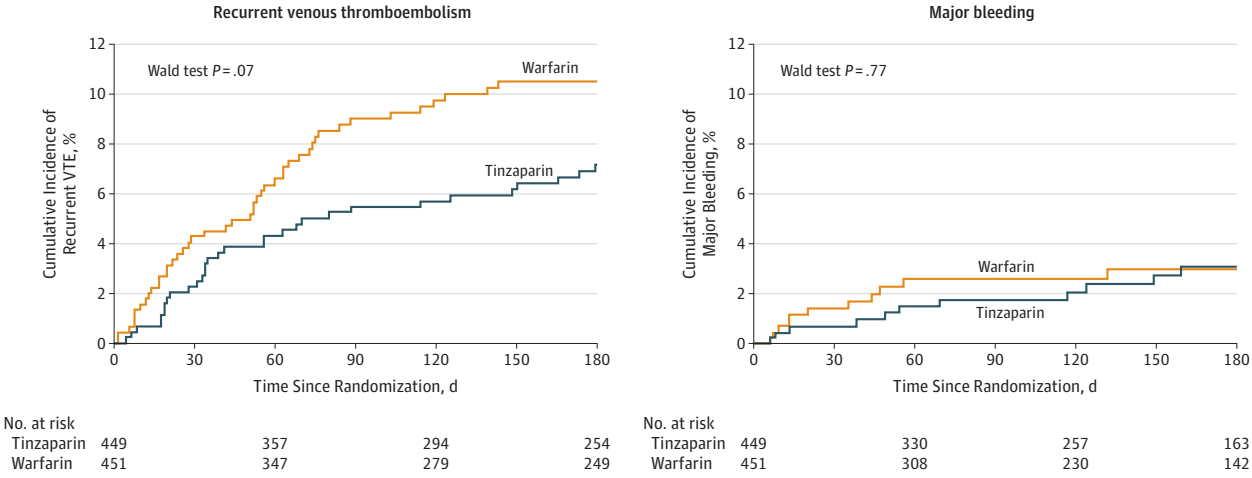
SI conversion factor: To convert creatinine clearance to mL/s/m^2, multiply by 0.0167.

[a] Patient may be receiving more than 1 type of cancer treatment.

[b] Includes cytotoxic, hormonal, targeted, and immunoregulatory therapy.

[c] Present within 3 months of randomization.

Figure 2. Cumulative Incidence Among Patients With Active Cancer According to Treatment With Tinzaparin vs Warfarin



VTE indicates venous thromboembolism. Source: The left panel of Figure 2 was reproduced with permission from the American Society of Hematology.[24]

Table 2. Primary and Secondary Efficacy and Safety Outcomes in the CATCH Trial

	No. (%)			
	Tinzaparin (n = 449)	Warfarin (n = 451)	HR (95% CI)	*P* Value
Primary Efficacy Outcome				
Recurrent VTE	31 (6.9)[a]	45 (10.0)	0.65 (0.41-1.03)	.07
Secondary Efficacy Outcomes				
Symptomatic DVT[b]	12 (2.7)	24 (5.3)	0.48 (0.24-0.96)	.04
Symptomatic nonfatal PE	3 (0.7)	2 (0.4)	NA	
Fatal PE[c]	17 (3.8)	17 (3.8)	0.96 (0.49-1.88)	.89
Incidental proximal DVT	0	1 (0.2)	NA	
Incidental PE	0	1 (0.2)	NA	
Recurrent VTE, per protocol, No./total patients (%)	29/351 (8.3)	39/307 (12.7)	0.62 (0.38-1.00)	.05
Safety Outcomes				
Major bleeding[d]	12 (2.7)	11 (2.4)	0.89 (0.40-1.99)	.77
Noncritical site	5 (1.1)	9 (2.0)		
Critical site	7 (1.6)	1 (0.2)		
Fatal bleeding[e]	0	1 (0.2)		
Clinically relevant nonmajor bleeding	49 (10.9)	69 (15.3)	0.58 (0.40-0.84)	.004
All bleeding	114 (25.4)	110 (24.4)	NA	
All-cause death	150 (33.4)	138 (30.6)	1.08 (0.85-1.36)	.54
Progression of cancer	105 (23.4)	93 (20.6)		
Fatal PE	17 (3.8)	19 (4.2)[f]		
Fatal bleeding[g]	3 (0.7)	3 (0.7)		
Other	25 (5.6)	23 (5.1)		

Abbreviations: DVT, deep vein thrombosis; HR, hazard ratio; NA, not available; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] One patient had a symptomatic nonfatal DVT and a symptomatic nonfatal PE on the same day.

[b] Of the 36 recurrent DVT events, 34 were proximal and 2 were distal. Both cases of distal recurrent DVT occurred in the warfarin group.

[c] The cause of death in all fatal PE cases was assigned by the central adjudication committee based on available data. None of the events had confirmatory imaging or autopsy results.

[d] Three patients had more than 1 major bleeding event during study period. Only the first event is included in the safety outcome analysis.

[e] Fatal bleeding events included in the safety outcome of major bleeding occurred from first dose of study drug to 24 hours after last dose of study drug.

[f] Two patients had a fatal PE after a recurrent DVT or PE and so there were 2 more fatal PE cases included here than in the efficacy outcome.

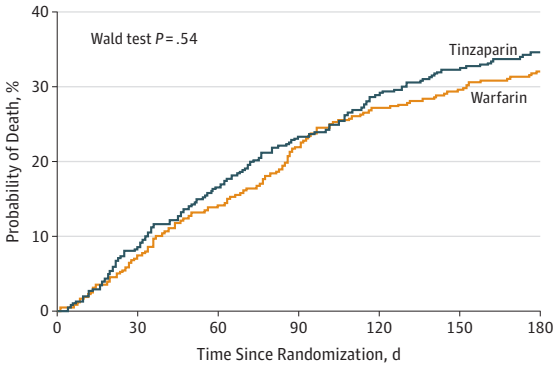
[g] Fatal bleeding events occurring any time during study period from randomization to death.

The significant reduction in symptomatic DVT and results of other secondary analyses should be considered hypothesis-generating and exploratory because we did not adjust for multiple comparisons. Study strengths include the international nature of the trial, with significant patient enrollment from countries outside of Europe and North America. Tinzaparin is available in 44 countries in Africa, Asia, Europe, Central, South and North America (except the United States) for the prevention and treatment of VTE.

The CATCH trial and previous LMWH trials in cancer-associated thrombosis share many study design characteristics. Like the Randomized Comparison of Low-Molecular-Weight Heparin vs Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial, which was previously the largest trial and established dalteparin as more efficacious than vitamin K antagonist therapy,[9,18] CATCH also used a prospective randomized open blinded endpoint (PROBE) design[19] and warfarin as the control comparator. Both studies used the same definition for active cancer, required the same eligible thrombotic events, and treated patients for 6 months. Unlike the CLOT trial, in which dalteparin was administered at a reduced dose after the first month, CATCH used tinzaparin at a full dose throughout the study period and included incidental VTE in its composite primary outcome. The rationale for similarities and differences in design features have been described.[13]

Lower than anticipated thrombotic event rates in the warfarin group of the CATCH trial may explain the differences in findings regarding the ability of LMWH to reduce the primary outcome in the CLOT trial vs the CATCH trial. Although we had expected a recurrence rate of 12.6% with warfarin, the observed rate was only 10.5%. This potentially affected the power of the trial to detect a benefit associated with tinzaparin. The lower risk may reflect critical differences in the patient populations between the CATCH vs CLOT trials. In the CATCH trial, fewer patients had metastatic disease (55% for CATCH vs 67% for CLOT), fewer had an ECOG performance status of 2 (23% for CATCH vs 36% for CLOT), fewer were receiving anticancer therapy (53% for CATCH vs 78% for CLOT), and fewer had a previous history of thrombosis (6% for CATCH vs 11% for CLOT). The 6-month mortality was also lower in CATCH compared with CLOT (32% for CATCH vs 39% for CLOT). Consequently, the CATCH population had fewer risk factors for thrombosis and recurrent thrombosis than the CLOT population. It is possible that a significant reduction in recurrent VTE might be observed with tinzaparin in a higher-risk population. Differences in geographic distribution, primary tumor sites, and associated anticancer treatments and the 10-year time gap between the 2 trials (during which cancer treatments have evolved) might also contribute to the discrepant findings. In both trials, the primary composite efficacy outcome was primarily comprised of symptomatic recurrent DVT, with a risk reduction of 52% in CATCH and 62% in CLOT. Fatal pulmonary embolism was also evenly distributed between

Figure 3. All-Cause Mortality Among Patients With Active Cancer According to Treatment With Tinzaparin vs Warfarin



No. at risk				
Tinzaparin	449	364	303	268
Warfarin	451	371	305	273

treatment groups, although it was slightly more common in CATCH than in CLOT. The low number of incidental thrombotic events in CATCH demonstrates the efficacy of anticoagulation.

The efficacy result difference between the CATCH and CLOT trials was unlikely due to differences in the degree of anticoagulation from warfarin therapy. The TTR was 47% in CATCH and 46% in CLOT and the time above INR therapeutic range was 27% in CATCH and 24% in CLOT. Although a TTR of 47% was low compared with trials in patients without cancer, it is consistent with the published literature and appears to be the achievable range for warfarin in patients with cancer who are susceptible to gastrointestinal toxicities, poor nutrition, and drug interactions.[8,10,20,21]

CATCH found a low risk of major bleeding in both treatment groups. Tinzaparin significantly reduced the risk of clinically relevant nonmajor bleeding compared with warfarin. Together with the adverse events data, CATCH demonstrated that tinzaparin, even when given at a full therapeutic dose for up to 6 months, is safe in a broad oncology population.[22]

The trial did not study the newer direct oral anticoagulants because they were not available when the study was designed. Our study results are still relevant because these agents are currently not recommended for use in patients with cancer by evidence-based consensus guidelines and warfarin remains the most commonly used anticoagulant worldwide for the treatment of cancer-associated thrombosis.[5,23] Further research is needed.

The trial has limitations. First, the sample size was insufficient because the incidence of recurrent VTE was lower than expected. Second, the open-label design is a source of potential bias. This design was chosen over double-blinding to avoid sham INR testing and sham injections, which increase patient anxiety. Providing realistic sham INR values is particularly challenging in an oncology population that may be affected by nutritional deficiencies,

chemotherapy treatment, and other comorbidities. Blinding might also compromise patient safety during episodes of thrombocytopenia and invasive procedures, and assessment of quality of life.[13] We attempted to minimize bias by using structured interviews during follow-up and blinded central adjudication. Third, approximately 5% of patients withdrew consent or were lost to follow-up. This is unavoidable in a population with advanced cancer. Fourth, this study was not designed to address potential differences in relative efficacy and safety of tinzaparin vs warfarin in subgroups of patients with cancer (eg, patients with different types of cancer).

Conclusions

Among patients with active cancer and acute symptomatic VTE, the use of full-dose tinzaparin (175 IU/kg) daily compared with warfarin for 6 months did not significantly reduce the composite measure of recurrent VTE and was not associated with reductions in overall mortality or major bleeding, but was associated with a lower rate of clinically relevant nonmajor bleeding. Further studies are needed to assess whether the efficacy outcomes would be different in patients at higher risk of recurrent VTE.

ARTICLE INFORMATION

Correction: This article was corrected for data errors in Table 2 on November 28, 2017.

Author Contributions: Dr Lee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lee, Kamphuisen, Meyer, Bauersachs, Janas, Khorana.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lee, Kamphuisen, Meyer, Bauersachs, Janas, Khorana.
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