Published in final edited form as: Evid Based Med. 2016 Apr;21(2):66. doi: 10.1136/ebmed-2015-110305

Category: Therapeutics

Study type:

Author's declarative title: Low-molecular-weight heparin for the treatment of acute venous thromboembolism in patients with active cancer

Citation: Lee AYY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA; for the CATCH Investigators. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer. A randomized clinical trial *JAMA* 2015;**314**:677-686

Commentary

Context

The management of acute venous thromboembolism (VTE) in patients with active cancer is challenging. In the landmark CLOT study[1], low-molecular-weight heparin (LMWH) halved the incidence of recurrent VTE compared to vitamin K antagonists (VKAs) with similar rates of major bleeding. These observations were confirmed in additional smaller studies which together with the more stable pharmacokinetics of LMWH has led to the recommendation of LMWH over VKAs [2,3]. Notwithstanding the favourable profile of LMWH, VKAs remain widely used world-wide. In this context, the results of the CATCH study were eagerly awaited.

Methods

The CATCH study was a two-arm parallel design randomized, open-label study with blinded central adjudication of study outcomes. 900 adult patients with active cancer and objectively documented VTE were randomized to 6 months of tinzaparin (175 IU/kg) once daily versus tinzaparin (175 IU/kg) once daily for 5 to 10 days followed by warfarin (target international normalized ratio 2.0 to 3.0). The primary efficacy outcome was a composite of recurrent symptomatic deep vein thrombosis (DVT), fatal or nonfatal pulmonary embolism (PE), and incidental VTE. Safety outcomes included major bleeding, clinically relevant non-major bleeding, and overall mortality. The results were reported as hazard ratio (HR) estimates with 95% confidence intervals (CIs). Overall, the trial design was strong with adequate concealment of allocation and statistical analyses according to the intent-to-treat principle.

Findings

The 6-month cumulative incidence of the primary outcome was 7.2% for tinzaparin vs 10.5% for warfarin (HR 0.65, 95%CI 0.41 to 1.03). There was a difference in symptomatic DVT (HR 0.48, 95%CI 0.24 to 0.96) but not PE (HR 0.96, 95% CI 0.49 to 1.88). The incidence of major bleeding was low and comparable between tinzaparin and warfarin (2.7% vs 2.4%; HR 0.89, 95%CI 0.40 to 1.99) while clinically relevant non-major bleeding was significantly reduced by tinzaparin (10.9% vs 15.3%; HR 0.58, 95% CI 0.40 to 0.84). Overall mortality was similar (33.4% vs 30.6%; HR 1.08; 95%CI 0.85 to 1.36).

Commentary

The CATCH study provides additional evidence on the efficacy and safety of LMWH for the treatment of acute VTE in cancer patients. A trend favouring full-dose tinzaparin over VKAs for recurrent VTE was observed, but the difference was smaller than anticipated, affecting the statistical power of CATCH. The rate of recurrent VTE in the tinzaparin was comparable to that observed with dalteparin in CLOT (7% vs 6%), whereas recurrent VTE in the warfarin group was lower than anticipated which could reflect critical differences between study populations. In CATCH, the prevalence of thrombotic risk factors (e.g. metastatic disease) was lower than in CLOT possibly resulting in a reduced risk of recurrent VTE. Another hypothesis for the lack of difference in efficacy could be a better control of VKAs therapy in CATCH, although this seems unlikely given the similar time in therapeutic range of VKAs.

As previously observed with dalteparin, tinzaparin was not associated with reductions or increased risks in major bleeding or overall mortality. Of note, the incidence of major bleeding in CATCH was numerically lower compared to CLOT both in LMWH (2.7% vs. 6%) and VKAs (2.4% vs 4%), again suggesting differences in study populations. Tinzaparin lowered the rate of clinically relevant non-major bleeding compared to VKAs, but CATCH was not powered to detect differences in safety outcomes.

Although we deem trials results valid, the “open design” puts the results at some risk of bias. The trialists attempted mitigating the potential for bias using blinded central adjudication of events, but we cannot exclude that the probability to detect an event through differential diagnostic work-up of, for example, clinically relevant non-major bleeding, was higher in the warfarin group due to lack of blinding of treating physicians. Adequate blinding may have attenuated observed differences even further.

Implications for practice

The CATCH study offers reassuring data on the safety of LMWH. Whether full dose regimens of LMWH other than tinzaparin have similar safety is unclear. The management of VTEs not included in the CATCH or CLOT studies (e.g. DVT of the upper extremities or splanchnic vein thrombosis) remains controversial.

Commentator details

Name: Marcello Di Nisio
Affiliation: University G. D'Annunzio
Correspondence address: University G. D'Annunzio, via dei Vestini, 66100 Chieti, Italy
Email: mdinisio@unich.it

and

Name: Anne W.S. Rutjes
Affiliation 1: Centre for Systematic Reviews at the Fondazione "Università G. D'Annunzio", Chieti, Italy
Affiliation 2: Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland.

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Competing interests
None.