

Tissue Factor As a Predictor of Recurrent Venous Thromboembolism in Malignancy: Biomarker Analyses of the CATCH Trial

Reference: Alok A. Khorana, Pieter W. Kamphuisen, Guy Meyer, Rupert Bauersachs, Mette S. Janas, Mikala F. Jarner, and Agness Y.Y. Lee.

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Abstract:

Purpose: Circulating tissue factor (TF) has been studied as a biomarker for predicting initial, but not recurrent, venous thromboembolism (VTE) in cancer, a setting in which predictors are incompletely understood. We evaluated the association of TF, clinical risk factors, and other biomarkers measured at the time of initial VTE with recurrent VTE in a prespecified analysis of the CATCH (Comparison of Acute Treatments in Cancer Hemostasis) trial.

Methods: CATCH was a randomized, multicenter trial that investigated tinzaparin 175 IU/kg once daily or dose-adjusted warfarin for 6 months in patients with cancer and acute, symptomatic VTE. TF ELISA, soluble P-selectin, D-dimer, FVIII, and C-reactive protein were assayed. Fisher's exact test was used to screen for association with VTE; competing risk regression analysis of time to recurrent VTE was conducted, accounting for multiple variables.

Results: The study population comprised 900 patients (recurrent VTE, n = 76; 8.4%). Of these patients, 805 had samples available for TF assay. Mean and median TF levels were 72.5 pg/mL and 50.3 pg/mL, respectively (range, 15.6 pg/mL to 4,798 pg/mL). Patients in the highest quartile of TF experienced the greatest VTE recurrence (> 64.6 pg/mL; 38 [19%] of 203 patients v 34 [6%] of 602 patients; relative risk, 3.3; 95% CI, 2.1 to 5.1; $P < .001$). In competing risk regression analysis of time to recurrent VTE, TF remained strongly associated with recurrent VTE (subdistribution hazard ratio [SHR], 3.3; 95% CI, 1.7 to 6.4). Other significant variables included venous compression from mass (SHR, 3.1; 95% CI, 1.4 to 6.5) and hepatobiliary cancer (SHR, 5.5; 95% CI, 2.3 to 13.6).

Conclusion: This is the first report, to our knowledge, to describe TF as a potential biomarker of recurrent VTE in patients with cancer who are on anticoagulation treatment. **A risk-adapted strategy could help identify high-risk patients who may benefit from more intensive anticoagulation approaches.**

Strengths:

- Pre-specified nature of secondary analysis
- Diverse study population (164 centres in 32 countries)
- Blinded, central adjudication of all outcomes (objective confirmation of recurrent VTE required)
- Intention to treat analysis
- Randomization was computer-generated and adequately concealed
- Randomization was stratified by tumor extent, geographic region, and history of VTE

Weaknesses:

- Trial was open-label (potential for harm and decreased patient quality of life if study was double-blinded)
- CATCH trial acknowledges that results of secondary analyses should be considered hypothesis-generating/exploratory (not adjusted for multiple comparisons)
- TF values were only drawn at time of acute VTE (difficult to apply results to TF ordered at any other time)
- TF was not collected at 16 of the sites due to lack of institutional ethics board or regulatory approval, some samples were not evaluable for biomarker tests due to shipping times from some sites
- Patients could have received up to 3 doses of LMWH before initiating the study (could cause variation in the measurement of biomarkers)
- Other bio-markers were also measured for fewer than the 900 study patients (782 for D-Dimer, 482 for CRP and soluble P-selectin)
- Patients with life expectancy <6 months were excluded from the study (somewhat limits applicability to palliative care), women of child-bearing potential were excluded from the study
- Mean time in therapeutic range (2-3) for warfarin arm was 47% (lower than trials in non-cancer patients but comparable with trials in cancer patients)
- 5% of patients withdrew consent or were lost to follow-up
- Different treatments/lack of treatment could affect results (this variable was not included in Table 1 of the CATCH trial)

Relevance to Palliative Care:

Results of this trial cannot be clinically applied yet (in palliative care or oncology), however the authors raise interesting questions that could be addressed with future research. If such results were validated and further characterized by more trials, values from a TF assay could potentially be used to aid in the estimation of a cancer patient's risk of recurrent VTE after an acute VTE. A validated biomarker, in the proper clinical context, could help tip the scale when weighing a palliative cancer patient's bleed and clot risk, deciding whether they require anticoagulation, and determining the dose and duration of their treatment.

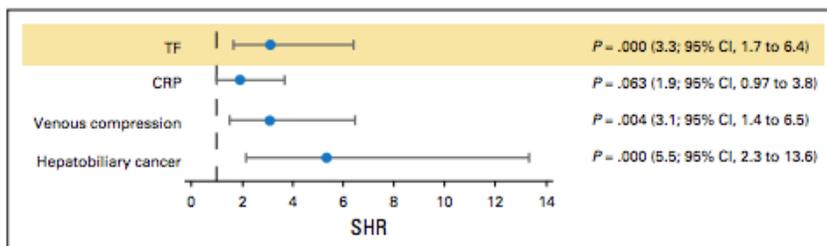


Fig 2. Subdistributional hazard ratios (SHRs; and 95% CIs) in the combined competing risk regression model. Competing risk regression analysis of time to recurrent VTE that accounts for study design variables and significant predictors identified in individual analyses. CRP, C-reactive protein; TF, tissue factor.