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Clinical utility of thrombin generation using ST-Genesia® instrument in patients with hereditary and acquired thrombophilia

Abstract Category: Hemostasis, transfusion medicine, vascular, laboratory medicine

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Introduction

The diagnostic utility of thrombin generation (TG) in patients with thrombophilia is unknown. We investigated the ability of TG to **discriminate** between patients with and without hereditary or acquired thrombophilia, to complement thrombophilia testing as a rule-out diagnostic tool in patients at high risk of arterial thrombosis or venous thromboembolism (VTE).

Methods

TG was measured in all **non-anticoagulated** patients who underwent thrombophilia testing for factor V Leiden (FVL), prothrombin gene G20210A mutation (PTM), protein C, S and antithrombin deficiency (PCD, PSD, ATD), and antiphospholipid antibody syndrome (APS) because of previous VTE, unexplained arterial thrombosis or a positive family history for VTE over the period of 3 years using **ST-Genesia® instrument/STG-Thromboscreen® assay.** To assess the screening utility of TG, we calculated the area under the receiver operating curve (AUC), and thresholds for 85%, 95% and 99% sensitivity, followed by associated positive and negative predictive values and likelihood ratios of each TG parameter for all investigated thrombophilias. To assess the **clinical utility,** cohort-related diagnostic failure rates (% of false negative) and the diagnostic yield (% in whom thrombophilia could be ruled out) were also calculated.

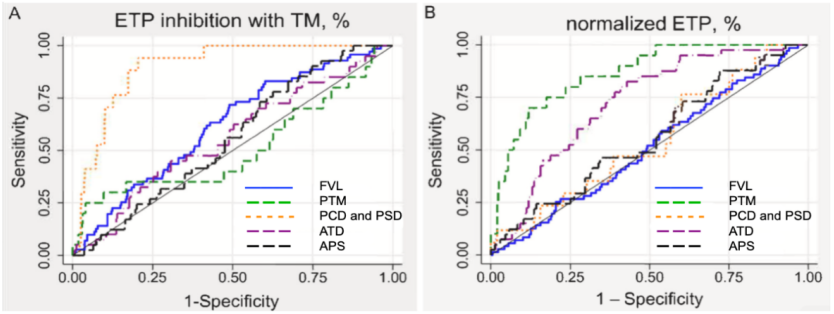
Results

Out of 804 screened patients, **467** (median age 43, interquartile range 32 – 56; 59% female) could be included in the analysis. Most patients were referred because of previous VTE (n = 283, 61%). Thrombophilia testing was positive in 161 patients (35%). Normalized endogenous thrombin potential (ETP) effectively discriminated for ATD (AUC =79 [95 %CI 72– 87]) and PTM (AUC 86 [95 %CI 79 – 93]) while ETP inhibition with thrombomodulin discriminated for PCD/PSD (AUC 90 [95 %CI 85– 95]) (Figure 1B, A). **Using the established best-performing TG parameter cut-offs (Table 1), PCD/PSD, PTM, ATD, and low-risk APS could be safely (<3 % failure rate) excluded in 62 %, 58 %, 27 %, and 29 % of cohort patients, respectively.**

Conclusion

TG assessment using ST-Genesia® system shows promise as a supportive screening tool in the thrombophilia work-up, safely avoiding further testing in at least a quarter of patients and reducing testing-related costs. Incorporating TG into the thrombophilia testing framework could enable a more individualised approach to the **diagnostic and clinical management** of patients with high thrombotic risk.

Figure 1. Diagnostic accuracy of ETP inhibition with TM (A), normalized ETP (B) for all investigated thrombophilias.



Abbreviations: APS, antiphospholipid antibody syndrome; ATD, antithrombin deficiency; ETP, endogenous thrombin potential; FVL, factor V Leiden; PCD, protein C deficiency; PSD, protein S deficiency; PTM, prothrombin gene G20210A mutation; TM, thrombomodulin.

Table 1. Overall diagnostic performance of clinical utility of selected thrombin generation parameter to exclude all types of investigated thrombophilias.

	TG parameter	Cutoff	Sensitivity (95 % CI)	NPV (95 % CI)	Negative LHR (95 % CI)	Post-test probability, % (failure rate)	Proportion of patients below the cutoff (yield, %)
Protein C and S deficiency	ETP + TM, nM/min	734.0	88.2 (65.7-97.7)	99.5 (98.1-99.9)	0.17 (0.05-0.62)	0.6	62.1
Antithrombin deficiency	Normalized ETP, %	87.3	97.5 (87.1-99.6)	98.9 (94.3-99.8)	0.09 (0.01-0.64)	0.8	26.8
Factor V Leiden mutation	ETP + TM, nM/min	470.0	85.9 (76.0-92.2)	92.1 (86.1-95.7)	0.48 (0.26-0.86)	7.8	27.2
Prothrombin gene G20210A mutation	Normalized ETP, %	102.0	90.0 (69.9-97.2)	99.3 (97.3-99.8)	0.17 (0.05-0.63)	0.8	57.8
Antiphospholipid antibody syndrome	Start tail ratio	0.98	95.1 (83.9-98.7)	98.3 (94.2-99.5)	0.17 (0.04-0.67)	1.6	29.1

Abbreviations: CI, confidence interval; ETP, endogenous thrombin potential; TM, thrombomodulin; TG, thrombin generation; PPV, positive predictive value, NPP, negative predictive value, LHR, likelihood ratio.

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