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Correlation of thromboelastography and thrombin generation assays in warfarin-treated patients

David E. Schmidt[a], Roza Chaireti[a,b], Maria Bruzelius[a,c], Margareta Holmström[a], Jovan Antovic[d], Anna Ågren[a,e,*]

[a] Department of Medicine, Division of Haematology, Coagulation Unit, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden
[b] Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[c] Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden
[d] Clinical Chemistry, Karolinska University Hospital, Molecular Medicine & Surgery, Karolinska Institutet, Sweden
[e] Department of Clinical Sciences, Danderyds Hospital, Division of Cardiovascular Medicine, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Venous thromboembolism (VTE) affects approximately 1 per 1000 persons annually. Although patients are increasingly treated with direct oral anticoagulants, many patients continue to be anticoagulated with vitamin K antagonists (VKA). The most important adverse events during VKA treatment, bleeding and the risk of recurrent VTE, are difficult to predict. Global haemostatic assays, such as thrombin generation assays and the viscoelastic whole blood tests thromboelastography (TEG) and thromboelastometry (ROTEM), allow a comprehensive assessment of haemostasis and could potentially predict such side effects.

In the present study we compared results from thrombin generation (Calibrated Automated Thrombogram and Innovance ETP assays) and TEG and ROTEM in 84 warfarin-treated patients with primary or recurrent VTE and 87 healthy controls. VKA treatment lead to lagtime prolongation and a lower overall thrombin production, which correlated strongly with INR (Pearson $r = 0.89$ and $r = -0.85$, respectively). The reduced thrombin generation of VKA-treated patients was accurately reflected by tissue-factor activated ROTEM (EXTEM) clotting time prolongation (vs. CAT lagtime, $r = 0.87$). Clot strength or clot formation kinetics were only weakly affected by thrombin generation. Intrinsic pathway activated TEG or ROTEM (INTEM) were not sensitive to the reduced thrombin generation.

In conclusion, patients anticoagulated with VKA after VTE showed a reduced plasma thrombin generation that was accurately reflected by tissue factor activated ROTEM. ROTEM provided additional information to thrombin generation, including clot formation kinetics and strength.

1. Introduction

The oral pharmacological management of venous thromboembolism (VTE), a common disease with an incidence of 1.0–1.8 per 1000 person years [1–3], consists of vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs). Despite an increase in the use of DOACs, many patients continue treatment with VKA. During VKA therapy, bleeding is the most common side effect, with severe bleeding occurring in an estimated 3% of patients, and a case fatality rate of 7% [4–7]. Recurrent VTE, another important complication, occurs in 3–8% of patients during VKA treatment [8,9].

Monitoring of anticoagulation effect during VKA treatment is performed in plasma with the international normalized ratio (INR), a simple and straightforward assay that can be implemented in routine settings and on point-of-care devices. INR's clot-based read-out occurs already when < 10% of total thrombin is formed and therefore incompletely represent the thrombin generation potential [10,11]. During INR measurement important factors that influence whole blood haemostasis, i.e. fibrinogen levels, fibrinolysis, red cell, platelet and leukocyte count or plasma volume, are not taken into account [12,13].

Global haemostasis assays, which assess anticoagulation and haemostatic capacity more extensively, could potentially provide useful information for the prediction of side effects during VKA treatment. An alternative to INR is the evaluation of plasma thrombin generation by thrombin generation assays (TGA), which provide information on the initiation, amplification and propagation of the coagulation cascade.

* Corresponding author at: Department of Clinical Sciences, Danderyds Hospital, Division of Cardiovascular Medicine, Karolinska Institutet, SE 182 88 Stockholm, Sweden.
E-mail address: anna.k.agren@sll.se (A. Ågren).

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VKA anticoagulation and INR prolongation is readily detected by TGA [14–16], and some studies indicate that TGA could predict recurrent VTE after discontinuation of anticoagulation [17,18].

Another alternative are the whole blood viscoelastic haemostasis assays thromboelastometry (ROTEM) and thromboelastography (TEG), which provide information on coagulation kinetics, clot strength, hypercoagulability and fibrinolysis. These tests benefit from point-of-care availability, the use of whole blood without a need for further sample processing, and rapidly available test results [19,20]. ROTEM has been shown to be sensitive for detection of hypercoagulability in VTE [21]. In addition, VKA anticoagulation is accurately detected by clotting time prolongation in tissue factor-activated whole blood coagulation assays [22,23], making it feasible to use these tests in VKA-treated patients.

In light of these divergent options, it remains currently unclear which test may provide more relevant or comprehensive information during anticoagulation treatment. Using a cohort of patients with VTE, the aim of the present study was to assess the correlation of plasma and whole blood global coagulation assays in VKA-treated patients, compared to controls. By using manual and semi-automatic TGA, TEG and ROTEM, we explored if plasma and whole blood tests could provide additional information upon another.

2. Materials and methods

This prospective observational study was approved by regional Ethics committee in Stockholm and conducted in accordance with the second declaration of Helsinki. All participants gave oral and written informed consent. The study population has been described previously [23]. In summary, warfarin-treated patients ($n = 107$) were recruited consecutively at the outpatient Coagulation Unit of Karolinska University Hospital, Stockholm, Sweden, and blood donors were included as healthy controls at the Karolinska University Hospital Blood Bank ($n = 89$). For the present study, patients were excluded if they were treated for other indications than primary or recurrent VTE ($n = 15$) (Fig. 1). Baseline characteristics, current medication use and a bleeding history were collected by a review of electronic medical records and a participant questionnaire. A clinical follow-up was performed for thrombotic and bleeding events by retrospective assessment of electronic medical records on March 2, 2018 (Supplementary Data).

2.1. Sample preparation and clinical chemistry

EDTA- and citrate anticoagulated blood was sampled from each participant after study inclusion by antecubital venipuncture. The procedure was similar for healthy controls and patients. Platelet poor plasma was prepared by centrifugation at 2000*g* for 15 min and stored within 30 min −70 °C for batch analysis of thrombin generation. Baseline laboratory tests, including complete blood count, aPTT, and fibrinogen were performed at the Department of Clinical Chemistry, Karolinska University Hospital. INR was determined using Owren method with the Spa + reagent from Stago (Asnieres sur Seince, Cedex France) on a Sysmex 2100i (Siemens Marburg, Germany) analyzer with EQUALIS (Uppsala, Sweden) calibrator.

2.2. Thromboelastography and thromboelastometry

Whole blood coagulation profiles were determined both by thromboelastography on a TEG 5000 unit (Haemoscope Corp.; Niles, IL, USA), using kaolin as an activator, and rotational thromboelastometry on a ROTEM delta system (TEM Innovations GmbH; Munich, Germany), employing three separate assays activated by either ellagic acid (INTEM reagent; TEM Innovations GmbH), tissue factor (EXTEM reagent; TEM Innovations GmbH) or tissue factor and the platelet inhibitor cytochalasin D (FIBTEM reagent; TEM Innovations GmbH), as previously described [23,24].

2.3. Thrombin generation assays

Frozen platelet poor plasma was thawed by immersion in a water bath at 37 °C immediately prior to analysis; the same procedure was followed for all the samples. Thrombin generation was then measured in two parallel assays.

First, thrombin generation was measured by the Calibrated Automated Thrombogram method (CAT®; Thrombinoscope BV, Maastricht, The Netherlands), according to manufacturer's instructions. Each sample was measured in triplicate. The final mixture of PPP reagent (trigger) and PPP used in the assay contained 5 pM tissue factor (TF) and 4 mM phospholipids. All reagents were obtained from Thrombinoscope BV, Maastricht, The Netherlands. 96-well plates were obtained from Ninolab, Stockholm, Sweden.

Secondly, thrombin generation was also measured as an automated test (Innovance® Endogenous Thrombin Potential [ETP]; Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) on a BCS® XP System (Siemens), according to the manufacturer's instructions. This test is activated by a combination of tissue factor and actin, activating both the intrinsic and extrinsic coagulation pathway (information by manufacturer). Thrombin generation curves were visualised and analysed using the manufacturers curve evaluation software. Intra-assay and inter-assay CVs for Pipetting Scheme C of the Innovance assay were 4.6 and 4.9%, respectively.

2.4. Statistical analysis and data sharing

Statistical analyses were performed using R version 3.3.1 (June 2016; available from https://www.R-project.org/). A two-sided *P*-value below 0.05 was interpreted as statistically significant. We encourage the request of the full study dataset for academic collaborations.

3. Results

From the study population of 181 individuals, ten individuals had an immeasurable result or technical failure (negative or oscillating thrombogram) and were excluded from further analyses. After this, the study included 84 VKA-treated patients and 87 healthy controls with a median age of 57.5 and 49 years, respectively (Table 1). All patients had VTE diagnosis as indication for VKA treatment with a median INR of 2.35 (interquartile range, 1.90–2.73). Other clinical and baseline laboratory data are presented in Table 1.

3.1. Tissue-factor activated thrombin generation

In both TGA assays used in this study, CAT and Innovance ETP, warfarin-treated patients had hypocoagulable thrombin generation profiles, characterised by a prolonged lagtime and time to peak, as well as reduced endogenous thrombin potential (ETP) and peak thrombin (all $P < 0.001$; Supplementary Fig. 1; Supplementary Table 1) in comparison to healthy controls. The manual CAT and the semi-automated Innovance assay showed a strong correlation of lagtime, time to peak, as well as ETP and peak thrombin levels (Fig. 2). CAT lagtime increased with age (rho = 0.29; Supplementary Table 2). Females showed a reduced CAT lagtime and time to peak and an increased thrombin peak (Supplementary Fig. 2). In contrast to CAT, the Innovance ETP assay showed no significant age- or sex dependency. We calculated reference intervals for CAT and Innovance assays using a weighted robust model and bootstrapping (Table 3). The reference intervals showed excellent segregation of patients and healthy controls at the indicated cut-offs for all TGA parameters, except for time to peak.

3.2. Correlation of baseline laboratory tests with thrombin generation

INR correlated firmly with lagtime, as well as a prolongation of the time to peak and a reduction in ETP and thrombin peak (Fig. 3A–B;

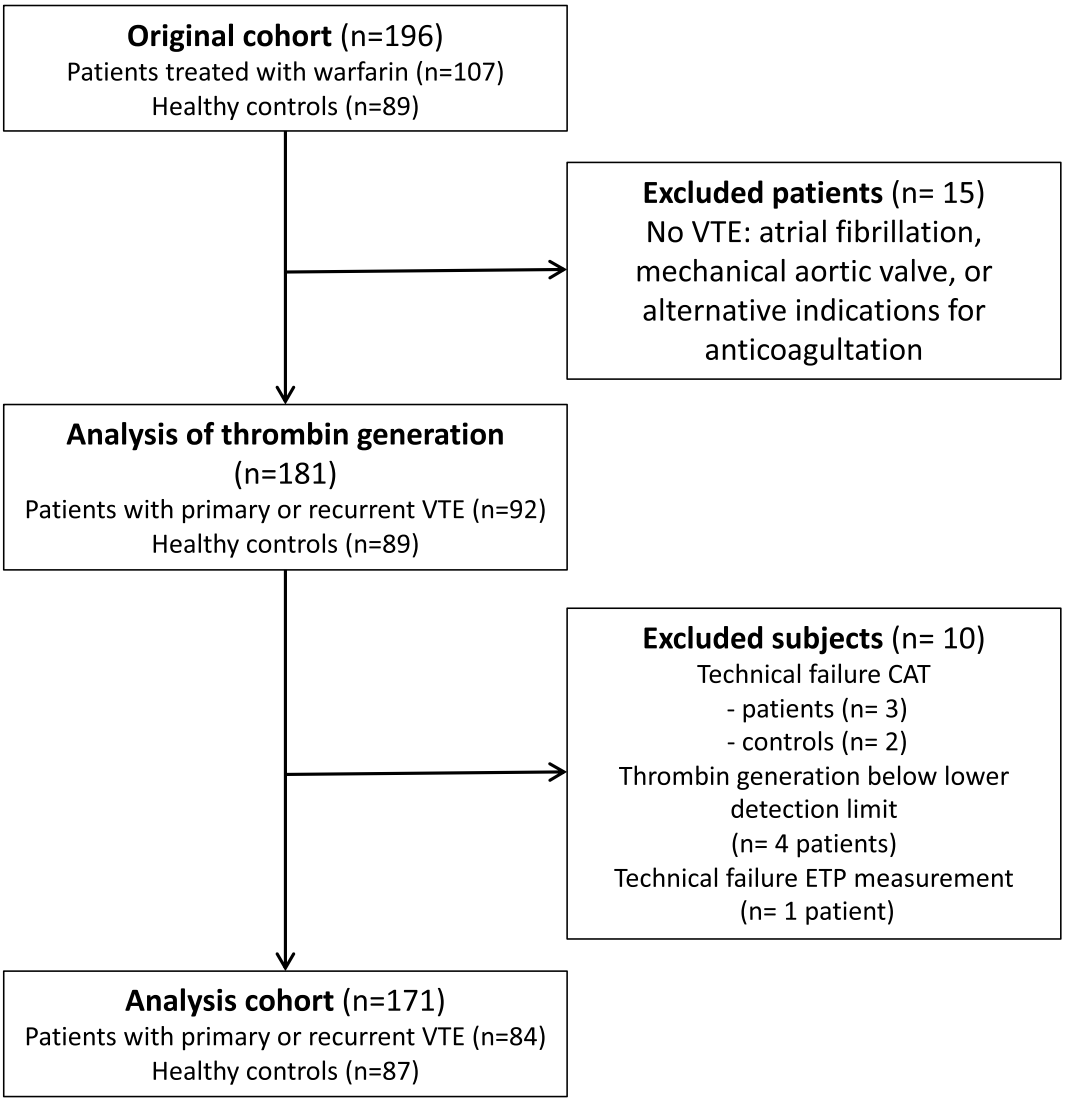

Fig. 1. Study flowchart.

Table 2). TGA results were only weakly affected by hemoglobin levels or leukocyte and platelet counts (Supplementary Table 3).

3.3. Correlation of thrombin generation with whole blood clot formation in TEG and ROTEM

We next investigated the association between coagulation profiles of plasma thrombin generation and whole blood using available data for ROTEM and TEG results together with the results of the TGA. A prolonged lagtime, just as INR, showed an excellent correlation with tissue factor-activated EXTEM clotting time prolongation (Fig. 3C–E). In ROTEM, the amplification of the clot production process is reflected by the clot formation time and alpha angle. We found only a weak-to-moderate relationship between TGA variables and the kinetic

Table 1
Baseline characteristics of the study population.

	Warfarin-treated patients (n = 84)	Healthy controls (n = 87)	P-value
Age, years	57.5 (48.5, 64.0)	49.0 (37.5, 56.0)	< 0.001
Male, n (%)	53 (63.1%)	50 (57.5%)	0.552
Hemoglobin (g/L)	141 (135, 151)	141 (135, 150)	0.698
Leukocyte count, $\times 10^{12}L^{-1}$	5.75 (4.88, 6.98)	5.60 (4.65, 6.50)	0.243
Platelet count, $\times 10^{9}L^{-1}$	232 (202, 264.00)	258 (231, 284)	< 0.001
aPTT, s	43.0 (38.0, 50.0)	33.0 (31.5, 36.0)	< 0.001
INR	2.35 (1.90, 2.73)	1.00 (1.00, 1.10)	< 0.001
Fibrinogen, g/L	3.2 (2.8, 3.5)	2.7 (2.4, 3.0)	< 0.001
Indication for anticoagulation			
Primary VTE, n (%)	42 (50%)		
Recurrent VTE, n (%)	42 (50%)		

Data presented as median (IQR) unless otherwise described. P-values are for a Wilcoxon rank sum test with continuity correction, or Pearson's Chi-square test for proportions.

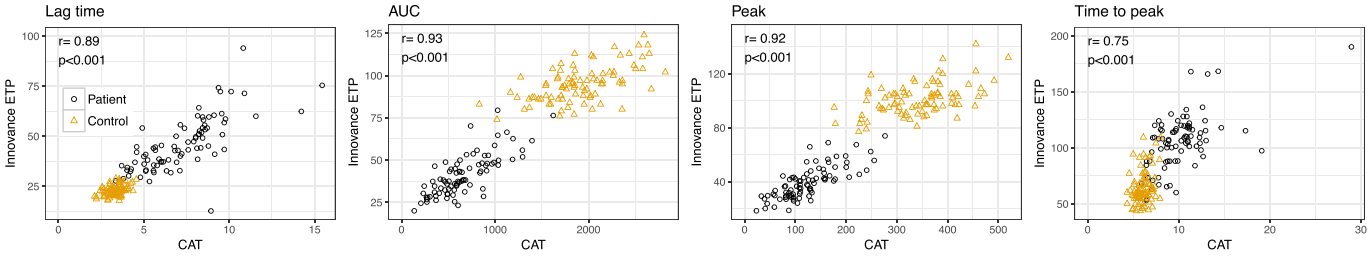

Fig. 2. CAT and Innovance ETP thrombin generation assays showed a high correlation (Pearson $r > 0.89$), except for time to peak (C).

parameters EXTEM CFT (Spearman rho ≤ 0.37) and EXTEM alpha (rho ≤ 0.12; Supplementary Fig. 3), indicating that the clot formation amplification process in the whole blood assay is only indirectly connected to thrombin formation. A graphical representation of the corresponding results of ROTEM, TEG and thrombin generation and their changes with increasing INR is presented in Fig. 4.

We also tested the correlation of intrinsic pathway activated whole blood viscoelastic assays and TGA. We observed a limited overlap of TEG and INTEM parameters with thrombin generation profiles (Supplementary Fig. 3; Fig. 4). Although TEG R-time and angle showed a moderate correlation with TGA parameters (Fig. 4), this was not uniform amongst patients with increased INR (Fig. 4).

As fibrinogen levels and platelet count were different between healthy controls and VKA treated patients (Table 1), we tested if the relationship between EXTEM CT and INR and TGA was dependent on these variables. After adjustment for fibrinogen levels, EXTEM CT was still significantly associated with INR (linear regression, Wald test; $P < 0.0001$) and CAT lagtime ($P < 0.0001$). EXTEM CT was not

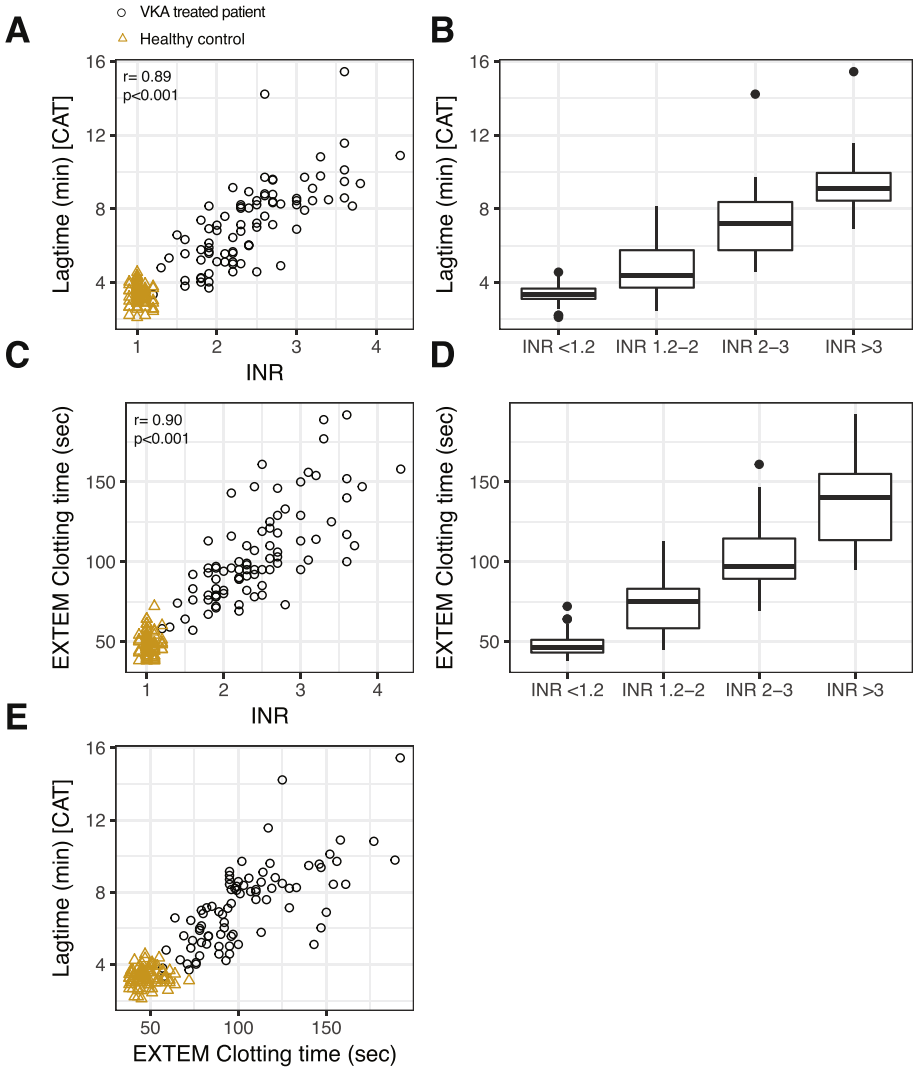

Fig. 3. Both thrombin generation and tissue factor activated ROTEM show a high correlation with INR values and excellent discrimination of healthy controls and VKA-treated patients (A–D). The prolonged start until thrombin production (lagtime) is accurately reflected by EXTEM clotting time. (E).

Table 2
Parameters of CAT thrombin generation and tissue factor activated ROTEM (EXTEM) correlate with INR.

	Correlation with INR
Lagtime	0.89
ETP	−0.85
Peak	−0.85
Time to peak	0.82
Clotting time (EXTEM)	0.90
Clot formation time (EXTEM)	−0.24
Alpha (EXTEM)	−0.11
Maximum clot firmness (EXTEM)	0.32

Pearson correlation coefficients.

influenced by platelet count.

4. Discussion and conclusions

A key clinical challenge for patients with venous thromboembolism is the prediction of side effects during vitamin K antagonist treatment, most importantly bleeding and recurrent thrombosis. The INR has several limitations, including a weak overall correlation with factors II and X [25], particularly at supratherapeutic INR levels [15,26], and an insensitivity to many secondary factors that contribute to the global haemostatic potential. Both TGA and ROTEM/TEG are potential candidates for improved diagnosis and prognosis in patients with thromboembolic disease on- or off-treatment with vitamin K antagonists [15,17,18,22,23,27,28].

In the present study assessed the correlation of thrombin generation and whole blood haemostasis assays of 84 patients with VTE who were treated with warfarin. Our data show that INR, thrombin generation lagtime and EXTEM clotting time are sensitive parameters for detecting effects of warfarin and correlate with each other. INTEM and TEG could not sensitively detect warfarin anticoagulation and had a low correlation with TGA results. Finally, both lagtime as total thrombin formation correlated highly between CAT and Innovance ETP thrombin generation methods, and we suggest they can be used interchangeably.

A choice for use of either TGA or EXTEM should be based on their predictive ability in clinical settings. Nonetheless, our data offer some indications as to which test to use. TGA parameters and EXTEM CT are highly correlated with INR, and it remains to be tested if the residual variation of any test shows an improved predictive potential over INR. In terms of prediction of thrombosis, kinetics and overall thrombin generation have been associated with thrombosis [17,18,29], which suggests that TGA could offer information on hypocoaguable as well as hypercoagulable states and may therefore be preferred. On the other hand, other determinants of the global haemostatic competence that are measured by EXTEM and have been associated with development of venous thrombosis such as clot formation kinetics and absolute clot firmness [30,31] did not correlate with TGA results or INR, indicating that these parameters do not directly depend on thrombin formation kinetics and may potentially provide additional information. In particular, we observed that EXTEM was also sensitive to platelet and fibrinogen levels, which are not included by thrombin generation assays.

Our data corroborate results of Nilsson et al., who showed similar changes of EXTEM and TGA coagulation profiles in warfarin-patients [32]. We expand on their work by comprehensively investigating the overlap of the two methods. In contrast, another study showed only a weak correlation between ROTEM and thrombin generation in healthy individuals [33], but here clot formation was not initiated by an activator, and the results are therefore expected to diverge from our study. Finally, Gatt et al. assessed thrombin generation in warfarin-treated patients with atrial fibrillation and showed similarly affected endogenous thrombin potential by CAT [16].

A strength of our study is the large study population and our comparison of in total 5 divergent global assays to determine individual coagulation profiles. Unfortunately, the study was not designed to provide sufficient outcome data for bleeding or thromboembolic events, and we therefore could not assess the predictive value of global haemostasis assays directly. A further limitation of our study was that we were not able to not test rapid TEG, a tissue factor activated assay that might show similar performance as EXTEM.

In conclusion, plasma thrombin generation in warfarin anticoagulated patients with VTE was accurately reflected by tissue-factor activated EXTEM. The thrombin generation assays CAT and Innovance ETP showed similar results, indicating that they may be used interchangeably. All TGA parameters were highly correlated with INR. EXTEM provided several parameters not correlated with INR, such as clot formation kinetics, clot firmness and lysis. Clinical studies are required to assess the potential of TGA and EXTEM parameters for prediction of side effects during VKA treatment.

Table 3
Reference intervals of thrombin generation parameters according to empirical 95% population level, robust weighted modeling with outlier removal, and ROC methods. Time to peak shows the least correspondence between cut-offs selected by the different methods, which is due to the relatively weaker separation between healthy controls and patients in this parameter.

	Empirical 95% (Lower; upper)	Robust (Lower; upper)	Outliers (*N*)	ROC (Max. J statistic)	J statistic	Comparison
Innovance ETP						
Lagtime	18.2; 28.3	17.4; 27.6	0	28.7	0.95	D > H
Time to peak	44.5;102.7	29.0; 91.4	0	80.2	0.72	D > H
AUC (%)	77; 118	73; 116	0	72	0.98	D < H
Cmax (%)	81; 130	76; 123	5	76	1.0	D < H
CAT						
Lagtime	2.3; 4.3	2.3; 4.3	0	4.4	0.89	D > H
Time to peak	4.6; 7.8	4.4; 7.7	0	7.6	0.79	D > H
ETP	1176; 2647	1097; 2712	1	1304	0.92	D < H
Peak	225; 472	198; 485	1	227	0.92	D < H

Outliers for the robust method were detected using the Horn method. The ROC cutoff was based on the highest Youden's *J* statistic that separated healthy controls from VKA-treated patients. Comparison, way of separation of values for ROC based cut-off, “D” for VKA-treated patients, “H” for healthy.

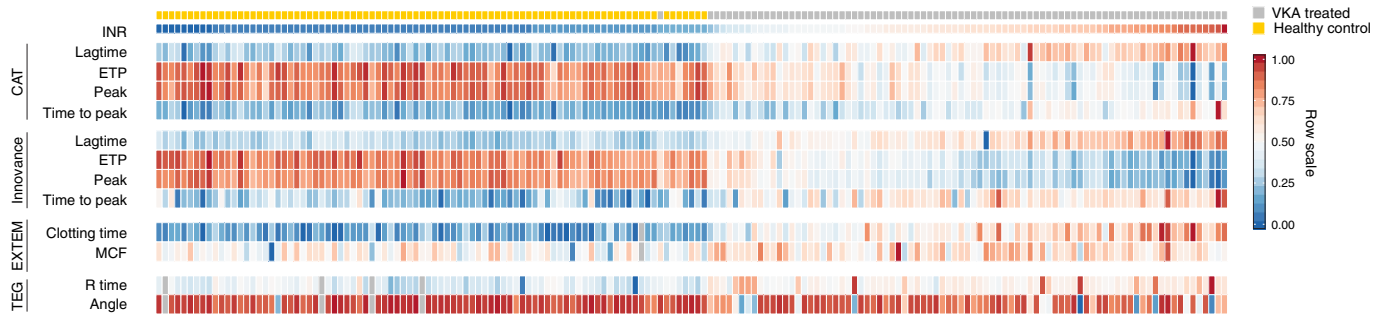

Fig. 4. Correlation of plasma and whole blood global haemostatic assays with INR in warfarin-treated patients and healthy controls. The heatmap shows how TGA, ROTEM and TEG change relative to each other with increasing INR. Each column represents test results from a single individual, ordered by INR from low to high. All parameter values were scaled per row from 0 to 1 (see scale) and the colour scheme centered at 0.50, such that low values are given in blue and high values given in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.03.022.

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