

**ORIGINAL ARTICLE**

# Fully automated thromboelastograph TEG 6s to measure anticoagulant effects of direct oral anticoagulants in healthy male volunteers

Ramin Artang MD<sup>1,2</sup>   | Maren Anderson MD<sup>1,3</sup> | Jorn D. Nielsen MD<sup>2</sup><sup>1</sup>Essentia Health St. Mary's Heart and Vascular Center, Duluth, Minnesota<sup>2</sup>Bispebjerg University Hospital, University of Copenhagen, Kobenhavn, Denmark<sup>3</sup>University of Minnesota School of Medicine, Minneapolis, Minnesota**Correspondence**

Ramin Artang, Essentia Health Saint Mary's Heart &amp; Vascular Center, 400 E Third St, Duluth, MN 55805-1984

Email: ramin\_artang@yahoo.com

**Abstract**

**Background:** The ability to assess the hemostatic effect of the direct oral anticoagulant (DOACs) may be valuable in clinical situations such as bleeding or thrombosis, before urgent surgery, or reversal of anticoagulation. We sought to assess the anticoagulant effect of DOACs with the new-generation fully automated thromboelastograph TEG 6s using resonance-frequency viscoelasticity measurements and disposable multichannel microfluidic cartridges.

**Methods:** A single dose of oral dabigatran 150 mg, rivaroxaban 20 mg, or apixaban 5 mg was given to 9 healthy males. Phlebotomy was performed at 0, 1, and 3 hours after administration of DOAC. TEG parameters were measured using TEG<sup>®</sup> 6s. Concentrations of DOACs were measured using chromogenic assays. The TEG parameters were correlated to the DOAC concentrations.

**Results:** The reaction time (R) demonstrated the strongest response to DOAC intake. There were no correlations between other TEG parameters and DOAC concentrations. Using the direct thrombin inhibitor (DTI) channel, R was significantly correlated with dabigatran levels ( $r = 0.94$ ,  $P < 0.0001$ ). Using the anti-factor Xa (AFXa) channel, R was significantly correlated with rivaroxaban and apixaban levels ( $r = 0.93$  and  $r = 0.83$ , respectively;  $P < 0.0001$  for both).  $R > 2.5$  minutes for dabigatran (DTI channel),  $> 2.5$  minutes for apixaban, and  $> 1.8$  minutes for rivaroxaban (AFXa channel) were associated with 100% sensitivity and  $\geq 90\%$  specificity to detect DOAC levels of  $\geq 50$  ng/mL.

**Conclusion:** We have demonstrated that TEG<sup>®</sup> 6s R has significant correlation with DOAC blood concentrations and has potential for monitoring the DOAC's effect on hemostasis with reasonable sensitivity in the small sample analyzed. This novel technology is easy to use on a small volume of whole blood without requiring a specialized laboratory. Further study is warranted to correlate R with clinical outcomes.

**KEYWORDS**

apixaban, dabigatran, direct oral anticoagulants, rivaroxaban, thromboelastography

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## Essentials

- The thromboelastograph TEG<sup>®</sup> 6s is a new technology that applies resonance-frequency for measurement of blood viscoelasticity and uses disposable multichannel microfluidic cartridges.
- We studied the correlation of TEG<sup>®</sup> 6s parameters to direct oral anticoagulant (DOAC) levels in 9 healthy volunteers after oral intake of DOACs.
- TEG<sup>®</sup> 6s reaction time demonstrated highly significant correlation with dabigatran, rivaroxaban, and apixaban blood concentrations.
- The reaction time demonstrated high sensitivity and specificity to detect DOAC concentrations of  $\geq 50$  ng/mL.

## 1 | INTRODUCTION

The direct oral anticoagulants (DOACs) are gaining ground among both patients and clinicians for their ease of use with fixed daily doses without the need for repeated testing of the coagulation. The ability to assess the hemostatic effect of the DOACs may be valuable in clinical situations such as bleeding or thrombosis, before urgent surgery, or reversal of anticoagulation.<sup>1,2</sup> At present, there are no assays approved for clinical use in the United States. DOAC-specific assays are used for research purposes in the United States and for both clinical and research use in the other parts of the world.

Thromboelastography (TEG) is a point-of-care test for global evaluation of hemostasis. It measures the viscoelastic properties of clotting blood *ex vivo*. Changes in viscoelastic properties depend on the amount and interaction of platelets and fibrinogen and the fibrin formation rate.<sup>3</sup> The previous generations of this technology, TEG<sup>®</sup> 3000 and 5000, have been extensively used to monitor hemostasis in patients having orthotopic liver transplantation and open heart surgery, in addition to routine coagulation tests in management of peri- and postoperative bleeding, and to reduce infusion of blood products.<sup>4,5</sup>

There are limited clinical data on the antithrombotic effect of DOACs. Most published data are from *in vitro* experiments testing the correlation of increasing drug concentrations and reaction time (R).<sup>6-8</sup> The majority of these studies were performed on TEG<sup>®</sup> 5000 using a kaolin assay. The TEG<sup>®</sup> 5000 with kaolin assay had a number of limitations, including the need for experienced operators and manual mixing of citrated blood with kaolin or other reagents prior to analysis. The technology was inherently sensitive to vibration. Finally, the kaolin assay was less sensitive to the effect of apixaban as compared to dabigatran and rivaroxaban.<sup>9</sup> The TEG<sup>®</sup> 6s (Haemonetics Corporation, Braintree, MA) is a new, fully automated 4-channel instrument. The system is less sensitive to vibration and employs multichannel microfluidic cartridges, eliminating manual mixing of any type prior to sample analysis. This new technology has been described in detail by Gurbel et al<sup>10</sup>. To date, there is only 1 study by Bliden et al<sup>11</sup> on the application of this technology to assess the anticoagulant effects of the DOACs. The study used blood from 26 healthy volunteers to obtain a normal range and compared it to blood from patients on dabigatran, rivaroxaban, and apixaban at a single time point. The DOAC concentrations were not measured. The study was a technical validation study of the TEG<sup>®</sup> 6s system and demonstrated  $\geq 92\%$  sensitivity and  $\geq 95\%$  specificity in identifying

patients on DOAC therapy using TEG<sup>®</sup> 6s R. The observations on other TEG parameters were not displayed.

The aim of this study was to evaluate the anticoagulant effect of dabigatran, rivaroxaban, and apixaban on TEG<sup>®</sup> 6s parameters by performing repeated measurements over time and to establish correlations with the drug concentrations used for treating atrial fibrillation or venous thromboembolism. The study furthermore intended to better define effects of administration of these agents on the TEG parameters and to demonstrate capability of TEG<sup>®</sup> 6s parameters for measurement of DOACs.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

The study was approved by the local institutional review board and was performed in accordance with the Helsinki II declaration. We enrolled men between 18 and 70 years of age who had normal laboratory screening test results, no abnormalities on physical examination, and normal vital signs. All participants provided written informed consent. The rationale for including only men was to avoid unpredictable interaction between the hormonal cycle and coagulation status among female subjects of reproductive age. Laboratory screening included renal and hepatic function, hepatitis B virus, hepatitis C virus, HIV serology, a complete blood cell count, prothrombin time, and activated partial thromboplastin time. Exclusion criteria were as follows: use of aspirin or nonsteroidal anti-inflammatory agents, history of allergy to blood products, a personal or family history of coagulation disorders, participation within 30 days in another research study, and any medication use within 7 days of the start of the study. Each subject received a single dose of 150 mg of dabigatran, 20 mg of rivaroxaban, or 5 mg of apixaban at different time points with at least 2 weeks between tests to allow for a washout period. Dose selection was based on standard doses recommended for treating atrial fibrillation and venous thromboembolic disease. Blood samples were obtained at time 0 before intake of the anticoagulant, and then 1 and 3 hours later. Phlebotomy was performed without a tourniquet. Samples for coagulation analysis were collected in a standard blue-top citrated tube (buffered sodium citrate 0.109 mol/L 3.2%, BD Vacutainer, Franklin Lakes, NJ). Samples were centrifuged at 7200 rpm/4400 g for 3 minutes.<sup>12</sup> Platelet-poor plasma was kept at  $-80^{\circ}\text{C}$  before being used in batch analysis for DOAC concentrations.

## 2.2 | Thrombelastography

The principles of the thromboelastographic measurement were previously described.<sup>3</sup> The basic TEG parameters include the R and coagulation time (K) in minutes, the angle of alpha in degrees, and the maximum amplitude (MA) in mm. Because both K and angle of alpha express the speed of clot formation, we chose to display only the angle of alpha and not the K in the present paper and as previously discussed.<sup>13</sup> We used the thrombelastograph TEG<sup>®</sup>6s. The details of this new technology have been described previously by Gurbel et al<sup>10</sup>. The TEG<sup>®</sup>6s applies resonance-frequency to vibrate a very thin layer of blood dispersed over a miniature ring inside the cartridge system. The degree of fluctuation of this film of blood is correlated to its viscoelasticity and is displayed over time as the blood clots. This technology, with the use of the premixed disposable multichannel microfluidic cartridges, is in contrast to the previous models' torsion wire with pins and cups. A citrated whole blood sample (0.6-0.7 mL) is pipetted into the entry port of the cartridge, which directs the blood into 4 separate analysis channels each containing different dried reagents based on the type of cartridge used. The global hemostasis cartridge that is currently commercially available contains kaolin in channel 1, kaolin with heparinase in channel 2, tissue factor and kaolin in channel 3 (RapidTEG channel), and abciximab and kaolin in channel 4 (functional fibrinogen channel). The cartridge used for the purpose of this test has kaolin in channel 1 (the citrated kaolin [CK] channel), ecarin in channel 2 (the direct thrombin inhibitor [DTI] channel), factor Xa in channel 3 (the antifactor-Xa [AFXa] channel) and abciximab with kaolin in channel 4 (the functional fibrinogen channel). This particular cartridge is currently not commercially available and is under investigation for use on patients who are anticoagulated with DOACs. All TEG analyses were performed within 30 minutes of the phlebotomy.

## 2.3 | Measurement of DOAC concentrations

Plasma was separated from each sample. We used chromogenic anti-FXa assays for rivaroxaban and apixaban (BIOPHEN DiXal, HYPHEN BioMed, Neuville-sur-Oise, France) and chromogenic anti-factor IIa assay (BIOPHEN<sup>™</sup> DTI, HYPHEN BioMed, Neuville-sur-Oise, France) for dabigatran. The analysis was performed on Siemens BCS XP R470570 (Siemens, Munich, Germany) and in accordance with the manufacturer's instructions by experienced laboratory technicians. Low calibrators were applied on samples with concentrations  $\leq 100$  ng/mL and standard calibrators for samples with concentration of  $>100$  ng/mL for all 3 DOACs.

## 2.4 | Statistical analysis

We determined the correlation of TEG parameters (R, alpha, and MA) with DOAC concentrations using Pearson's correlation coefficient and linear regression models.

Alteration of each TEG parameters over time was analyzed for each DOAC agent using repeated-measures analysis of variance. All data

were presented as mean and standard deviation (SD), unless otherwise indicated.  $P < 0.05$  (2-tailed) was considered statistically significant.

The clinically relevant DOAC concentration cutoffs based on current available literature are 30 ng/mL for urgent invasive procedures with high bleeding risk,<sup>14</sup> ng/mL for antidote administration<sup>15</sup> and 100 ng/mL for thrombolysis in stroke.<sup>16</sup> The receiver operating characteristic curve was calculated for sensitivity and specificity of R for these concentrations of DOAC agents. We used Prism software version 8 (GraphPad Software Inc., La Jolla, CA) and MedCalc version 14.12.0 (MedCalc Software bvba, Ostend, Belgium) for data analysis.

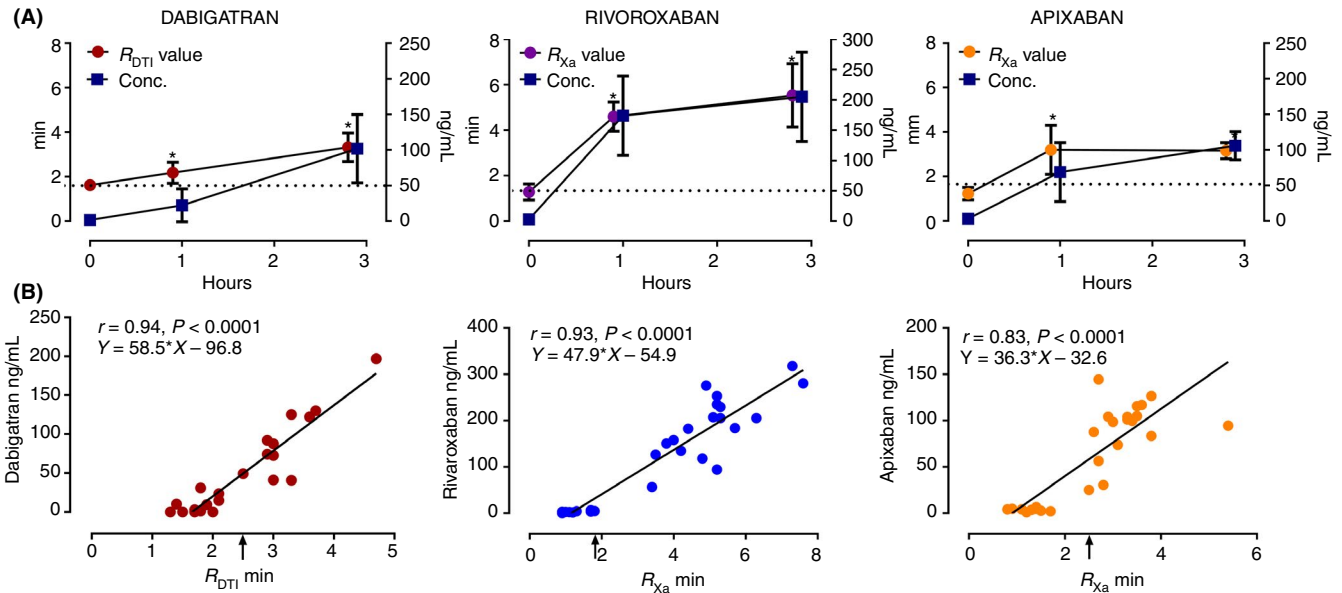
## 3 | RESULTS

Nine healthy male volunteers (mean age,  $41 \pm 12$  SD; median, 39; and range, 25-59 years old) enrolled in the study. In the present study, the highest concentrations for dabigatran were achieved at 3 hours, with mean concentration of  $102$  ng/mL  $\pm 48$  SD (median,  $92.1$  ng/mL; total range, 40.7-196.9). For rivaroxaban the highest concentrations were achieved at 3 hours, with mean concentration of  $205.2$  ng/mL  $\pm 73.7$  SD (median,  $205.5$  ng/mL; total range, 94.2-317.9). For apixaban the highest concentrations were achieved at 3 hours, with mean concentration of  $105$  ng/mL  $\pm 19.7$  SD (median,  $104.2$  ng/mL; total range, 73.8-144.5) (Figure 1A).

The alteration of TEG<sup>®</sup>6s parameters R, alpha, and MA over 3 hours after intake of a single dose of DOAC is displayed in Table 1. R was significantly increased at 1 and 3 hours after administration (Table 1 and Figure 1A). The scatter diagrams of DOAC concentrations against R are displayed in Figure 1B. The R was strongly correlated with DOAC concentrations ( $r = 0.94$  for dabigatran using DTI channel,  $r = 0.93$  for rivaroxaban,  $r = 0.83$  for apixaban using AFXa channel;  $P < 0.0001$  for all). The deviation of alpha from baseline was minimal but statistically significant at 3 hours for both dabigatran using the DTI channel and apixaban using the AFXa channel. The MA had no significant deviation from baseline. There were no significant correlations between DOAC concentrations and K, alpha, or MA. To demonstrate the advantage of the DOAC-specific cartridge as compared to standard CK assay, R from the CK channels ( $R_{CK}$ ) were displayed in Table 1. The  $R_{CK}$  times for dabigatran and rivaroxaban were significantly increased as compared to baseline but not to the same extent as the DOAC-specific channels. The  $R_{CK}$  times for apixaban were not significantly increased at peak apixaban concentrations.

The total analysis time to obtain all TEG parameters including R, alpha, and MA once the sample had entered the TEG device was 30 to 50 minutes. If the focus was to obtain the isolated R value, the analysis time was as indicated in Table 1 within 3 to 7 minutes of the analysis start.

The sensitivity and specificity of the R to detect dabigatran concentrations  $\geq 30$ ,  $\geq 50$ , and  $\geq 100$  ng/mL using DTI channel, rivaroxaban and apixaban concentrations  $\geq 30$ ,  $\geq 50$ , and  $\geq 100$  ng/mL using the AFXa channel are displayed in Table 2.



**FIGURE 1** (A) The DOAC concentrations and the effect on TEG 6s R. \*Indicates  $P < 0.05$  compared to baseline level at time 0. The bars represent mean  $\pm$  SD. (B) The scatter diagram of DOAC concentrations against R. The dotted line represents the 50 ng/mL threshold of the DOAC concentrations. The arrow represents the R value above which the subject is considered to have DOAC concentrations at or above 50 ng/mL for the 3 DOACs examined.  $R_{DTI}$  indicates using the DTI channel;  $R_{Xa}$  indicates using the AFXa channel

**TABLE 1** Alteration of TEG 6s parameters over time after oral intake of single dose of DOAC

Agent	Parameter	Hours after intake			P-value	Max change from baseline in % $\pm$ SD
		0	1	3		
Dabigatran <sup>a</sup>	Conc. (ng/mL)	<5 <sup>c</sup>	22.3 $\pm$ 23.3	102 $\pm$ 47.9	0.0001	
	$R_{DTI}$ (min)	1.6 $\pm$ 0.2	2.2 $\pm$ 0.5	3.3 $\pm$ 0.6	<0.0001	106.3 $\pm$ 35
	Alpha (degrees)	72.4 $\pm$ 1.2	72.9 $\pm$ 1.2	73.8 $\pm$ 1.0	0.004	2.1 $\pm$ 1.2
	MA (mm)	63.0 $\pm$ 2.5	63.3 $\pm$ 2.3	63.5 $\pm$ 1.8	ns	0.9 $\pm$ 1.6
	$R_{CK}$ (min)	6.8 $\pm$ 1.0	8.8 $\pm$ 1.7	12.7 $\pm$ 2.4	<0.0001	89 $\pm$ 37.6
Rivaroxaban <sup>b</sup>	Conc.	<5 <sup>c</sup>	174.1 $\pm$ 65.5	205.2 $\pm$ 73.7	<0.0001	
	$R_{Xa}$	1.3 $\pm$ 0.4	4.5 $\pm$ 0.7	5.6 $\pm$ 1.5	<0.0001	354.5 $\pm$ 108
	Alpha	72.4 $\pm$ 1.0	74.0 $\pm$ 0.8	73.6 $\pm$ 1.8	ns	2.1 $\pm$ 2.7
	MA	61.2 $\pm$ 1.3	62.0 $\pm$ 1.7	61.7 $\pm$ 1.4	ns	1.1 $\pm$ 1.3
	$R_{CK}$	6.5 $\pm$ 1.1	10.0 $\pm$ 1.2	11.6 $\pm$ 2.0	<0.0001	83.7 $\pm$ 49.6
Apixaban <sup>b</sup>	Conc.	<5 <sup>c</sup>	68.8 $\pm$ 41.4	105.9 $\pm$ 19.7	<0.0001	
	$R_{Xa}$	1.2 $\pm$ 0.3	3.2 $\pm$ 1.1	3.2 $\pm$ 0.4	<0.0001	209.3 $\pm$ 97
	Alpha	71.8 $\pm$ 1.8	73.2 $\pm$ 1.5	73.6 $\pm$ 1.0	0.004	2.7 $\pm$ 2.1
	MA	60.3 $\pm$ 2.2	60.3 $\pm$ 1.9	60.8 $\pm$ 1.9	ns	0.4 $\pm$ 3.0
	$R_{CK}$	6.9 $\pm$ 0.8	8.4 $\pm$ 1.7	7.9 $\pm$ 1.0	ns	15.7 $\pm$ 18.4

AFXa, antifactor-Xa; DTI, direct thrombin inhibitor; MA, maximum amplitude; R, reaction time; SD, standard deviation.

<sup>a</sup>Indicates using the DTI channel.

<sup>b</sup>Indicates using the AFXa channel. The values indicated mean  $\pm$  SD.

<sup>c</sup>Mean levels were below the lower limits of detection defined by the manufacturer.

## 4 | DISCUSSION

To our knowledge, this is the first study to evaluate the utility of TEG<sup>®</sup> 6s in assessment of the anticoagulant effect of the most commonly used DOACs, dabigatran, rivaroxaban, and apixaban, through

serial measurements over time. The TEG parameters were correlated with DOAC concentrations using cartridges specifically designed for this purpose containing ecarin and factor Xa in order to increase its sensitivity to DTI and AFXa inhibitors, respectively. We have demonstrated that R is the most sensitive TEG parameter to alterations

**TABLE 2** Sensitivity and specificity of R to detect DOAC concentrations above thresholds mentioned

DOAC	Threshold (ng/mL)	R (min)	Sensitivity	Specificity	AUC
Dabigatran <sup>a</sup>	30	>2.1	92 (61.5-99.8)	100 (78.2-100)	0.96
	50	>2.5	100 (63.1-100)	90 (66.9-98.7)	0.95
	100	>3	100 (39.8-100)	96 (78.1-99.9)	0.99
Rivaroxaban <sup>b</sup>	30	<sup>c</sup>			
	50	>1.8	100 (81.5-100)	100 (66.4-100)	1.00
	100	>3.4	100 (79.4-100)	91 (58.7-99.8)	0.95
Apixaban <sup>b</sup>	30	>2.5	100 (79.4-100)	100 (71.5-100)	1.00
	50	>2.5	100 (78.2-100)	92 (61.5-99.8)	0.98
	100	>2.6	100 (63.1-100)	63 (38.4-83.7)	0.84

AFXa, antifactor-Xa; AUC, area under the curve; DOAC, direct oral anticoagulant; DTI, direct thrombin inhibitor; R, reaction time.

The values in parentheses indicate 95% confidence interval.

<sup>a</sup>Indicates using the DTI channel.

<sup>b</sup>Indicates using the AFXa channel.

<sup>c</sup>Due to no acquired concentrations between 30 and 50 ng/mL, no calculations could be obtained.

in hemostasis by the DOACs. R demonstrated significant correlation with DOAC concentrations. We have furthermore demonstrated that R has useful sensitivity and specificity to detect low DOAC concentrations in this small sample of healthy volunteers. This function is potentially useful beyond situations mentioned in the Introduction section such as presurgical patients on DOAC with uncertainty about their hemostatic function, or prior to direct-current cardioversion or radiofrequency ablation procedures in patients with atrial fibrillation with uncertainty about the adequacy of anticoagulation. As the “therapeutic ranges” for these agents are not yet defined, increased R above a certain threshold using the DTI channel for patients on dabigatran and AFXa channel for patients on AFXa inhibitors may provide useful information on the concentrations of these agents being below or within the range observed in the major clinical trials with the DOACs.

The TEG<sup>®</sup>6s applies resonance-frequency viscoelasticity measurements and premixed disposable multichannel microfluidic cartridges to bypass the limitations of its prior models. This point-of-care device can provide the measurements on whole blood and eliminates the need for centrifugation. The analyses in the present study were performed within 30 minutes of the phlebotomy, as the subjects examined were not acutely ill. In practice, when dealing with acutely ill patients, the analysis can be performed immediately after phlebotomy. Once the analysis was started, the R times were resulted within 3 to 7 minutes as indicated in Table 1. The turnaround times, or time from receiving the blood sample in the lab to first result published, were not calculated, as the subjects were already present in the laboratory and the workflow was not representative of the clinical situation. In acute stroke patients, Seiffge et al<sup>16</sup> were able to measure DOAC concentrations with median turnaround time of 35 minutes (29-75 minutes) using the same chromogenic assays that were used in the present study. To achieve these numbers, their laboratory had these assays available 24 hours a day. Thrombin generation assay in its current format takes up to 2 hours for analysis of DOAC specimens in specialized laboratories.<sup>17</sup> The TEG<sup>®</sup>6s analysis time can

therefore be considered competitive in regards to the time efficiency as compared to the other methods currently under investigation.

The baseline values for the reaction time in the present study ( $1.6 \pm 0.2$  minutes for the DTI channel,  $1.3 \pm 0.3$  minutes for the AFXa channel) are compatible with the preliminary reference range established by Bliden et al<sup>11</sup> ( $1.5 \pm 0.2$  minutes for the DTI channel and  $1.3 \pm 0.3$  minutes for the AFXa channel) suggestive of consistency in the measurements. At this point, no final reference range has been established by the manufacturer but is in process and will be published soon. The other TEG parameters, alpha, K, and MA, were not substantially altered irrespective of the type of TEG channel applied.<sup>8</sup> This observation is in contrast to the effect of the heparins and warfarin on TEG parameters. The latter agents not only prolong R but also reduce alpha and MA.<sup>2,13</sup> This observation reflects the effect of the DOACs on primarily prolonging the whole blood clotting time as opposed to speed of clot formation or the interaction between platelets and fibrinogen.

Limitations of this study include the small number of younger healthy volunteers, rather than patients with atrial fibrillation or thromboembolic disease. The study was furthermore limited due to use of only 3 time points over 3 hours rather than more time points over 12 to 24 hours. For the TEG<sup>®</sup>6s to demonstrate sensitivity and specificity for the presence of DOACs in blood at very low concentrations, future studies need to emphasize measurements at true trough levels. We evaluated only a single dose of the anticoagulants rather than repeated doses at steady-state drug concentrations. Peak concentrations achieved in the present study were within the range of concentrations documented in clinical studies with patients receiving DOACs for atrial fibrillation or thromboembolism, indicating that the single-dose regimen in the present study was sufficient to obtain adequate blood DOAC concentrations.<sup>18,19</sup> The thresholds for R to detect the lower range of DOAC concentrations, sensitivities, and specificities displayed in the present study need to be viewed with caution in this feasibility study on 9 healthy volunteers and were primarily to demonstrate proof of concept. It is expected

that these thresholds may change with a larger pool of healthy subject and patients on DOACs in larger studies under progress.

In conclusion, TEG<sup>®</sup>6s R has the ability to measure the DOACs' effect on hemostasis with significant correlation with DOAC concentrations among the agents examined in this study on healthy volunteers. This novel technology is easy to use with a small amount of whole blood and without the need for a specialized laboratory or expertise. Larger clinical studies on patients receiving therapeutic doses of DOACs are warranted to correlate R and adverse clinical outcome in order for this test to be clinically useful.

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## RELATIONSHIP DISCLOSURE

None of the authors have any disclosures relevant to this paper.

## AUTHOR CONTRIBUTIONS

RA was responsible for the design of the study, part of the laboratory analysis, statistical analysis, and writing the manuscript. MA was responsible for the data collection and interpretation of the data and revising the manuscript. JDN was responsible for design of the study and revising the manuscript.

## ORCID

Ramin Artang  <https://orcid.org/0000-0002-3408-9547>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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