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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Thromboelastography for predicting bleeding in patients with aortic stenosis treated with transcatheter aortic valve implantation

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Abstract

Background: Bleeding complications are frequent and independently impact mortality after transcatheter aortic valve implantation (TAVI). Thromboelastography (TEG) measures viscoelastic properties of clot formation and is currently best known for perioperative management to reduce blood transfusion in cardiac surgery.

Aim: We sought to determine whether TEG may be predictive of bleeding in patients treated with TAVI.

Methods and results: Overall, 54 consecutive patients with severe aortic stenosis treated with TAVI were prospectively included. In all patients, two blood samples were obtained for TEG measurement (the first — 12 h prior to procedure tested with citrated kaolin [CK] TEG assay, and the second — immediately after prosthesis deployment tested with CK and citrated heparinised kaolin assay [CHK]). Major or life-threatening bleeding (MLTB) was diagnosed in 13 (24%) patients. In receiver-operating characteristic (ROC) curve analysis the only TEG parameters showing significant sensitivity and specificity for predicting MLTB were those obtained in the CK sample at the end of the procedure: R value (reaction time, time to initiation of clot formation) area under the curve (AUC) 0.69, 95% confidence interval (CI) 0.49–0.88, p = 0.04; angle (the rate of clot formation), AUC 0.75, 95% CI 0.59–0.92, p = 0.007, and maximum amplitude (MA, ultimate strength of fibrin clot), AUC 0.77, 95% CI 0.62–0.93, p = 0.003. After controlling for confounding factors on multivariate logistic regression, MA remained as the only TEG parameter that significantly correlated with bleeding after TAVI, both as a continuous variable (p = 0.004; 95% CI 0.92–0.98; odds ratio [OR] 0.95 per 1 mm increment) and after using the cut-off value derived from ROC analysis; MA < 46.6 mm (OR 10.4; 95% CI 2.1–51.8; p = 0.004).

Conclusions: Low strength of fibrin clot measured by TEG immediately after TAVI may serve as an independent predictor of short-term major and life-threatening bleeding complications.

Key words: TAVI, TAVR, aortic stenosis; bleeding; TEG 5000, thromboelastography, maximal amplitude, major or life-threatening bleeding

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is now the treatment of choice for symptomatic patients suffering from severe aortic stenosis (AS), who are at high surgical risk or deemed inoperable. As proven previously, the method has shown similar prognostic benefits in high-risk groups of patients, and in recent studies it was shown that when performed through illio-femoral access, TAVI patients may have survival advantage in both high- and intermediate-risk groups when compared to surgical aortic valve replacement [1–4]. Although less invasive, the transcatheter procedure is also burdened with several complications, which may affect the final outcome. One of the most common adverse endpoints is major bleeding, which may occur in as many as 11–31% of patients [1–4]. High prevalence of these episodes may be due to both procedural and clinical contributing factors. On the clinical side, severe AS is associated with enhanced thrombogenicity due to increased tissue factor concentration within calcified aortic leaflets [5]. On the other hand, because of high-molecular-weight Von Willebrand factor multimer

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degradation, patients with severe AS may be exposed to higher bleeding risk [6]. But what is of uppermost importance is the heterogeneity of coagulation-affecting medications that is present in this cohort of patients. In clinical trials up to 33% of patients had a history of atrial fibrillation, 27–30% had previous percutaneous coronary interventions (PCI), and 18–28% had a previous myocardial infarction. Every one of these conditions requires a different antithrombotic strategy: single or dual antiplatelet therapy (SAPT, DAPT), or oral anticoagulation (OAC). To counter these underlying coagulation abnormalities appropriate periprocedural treatment is implemented. Current expert opinions suggest that during the procedure unfractionated heparin (UFH) should be used to maintain an activated-clotting time (ACT) of around 300 s [7] and afterwards dual antiplatelet therapy with aspirin and clopidogrel should be administered for one to six months for prevention of thromboembolic events [7–9].

Therefore, given the high complexity of periprocedural coagulation processes and many factors, which may alter its course, we hypothesised that the assessment of viscoelastic features may be useful in predicting bleeding. In the present study we used a point-of-care, whole blood sample thromboelastography (TEG) device to determine the impact of periprocedural thromboelastographic parameters on bleeding events after TAVI.

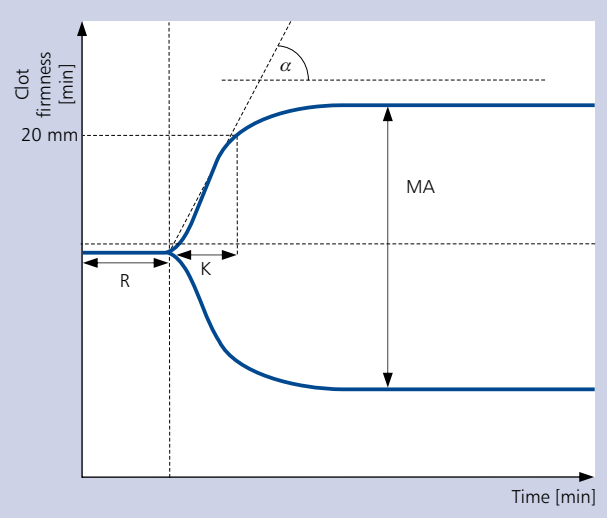

Figure 1. Normal thromboelastography tracing; R — reaction time, time of latency from start of test to initial fibrin formation; K — kinetics, time taken to achieve a certain level of clot strength (amplitude of 20 mm); MA — maximal amplitude, represents the ultimate strength of the fibrin clot; angle (α) — measures the speed at which fibrin build up and cross linking takes place, hence assessing the rate of clot formation

METHODS

Study design and population

The study was designed as prospective, single-centre, observational with in-hospital follow-up of events. The study population consisted of 54 consecutive patients with severe, symptomatic AS referred after a Heart Team decision to TAVI in the Department of Cardiology at the Medical University of Warsaw. In each patient two whole blood samples were obtained. The first was taken within 24 h prior to the procedure and analysed with citrated kaolin (CK) TEG assay. The second was taken after successfully obtaining the haemostasis at the access site, approximately 30 min after valve implantation, while the patient was still in hybrid operating room, and tested with both CK TEG and citrated heparinised kaolin (CHK) TEG assays. Basic blood morphology and coagulation test results of each patient were collected, as well as information regarding periprocedural anticoagulation treatment, the need for blood product transfusion, and volume of drainage in case of surgical access. Source data concerning bleeding events were collected throughout the hospital stay on a daily basis and entered into a specifically designed electronic database.

Thromboelastography

A point-of-care TEG® 5000 Thrombelastograph® Hemostasis Analyzer system (Haemonetics, MA, USA) was used. The test is generally performed by placing a cylindrical cup filled with a 360-μL sample of whole blood beneath a pin, which is suspended on a torsion wire. The cup then oscillates through an angle of 4°45′ within 10-s periods per cycle. After initialising the bond between fibrin and activated platelets the pin and the cup are linked together and the twisting force of the pin is converted to an electrical signal, which can be monitored. The resulting haemostasis profile is a measure of the time it takes for the first fibrin strand to be formed, the kinetics of clot formation, the strength of the clot, and its dissolution (Fig. 1). In the current study we used two types of test: CK TEG and CHK TEG. The first one is a standard TEG assays obtained into citrated test-tube to allow testing within 2 h after taking the blood sample. The second type of test was additionally carried out in a cup with heparinase to remove the effect of UFH. In both types of tests 340 μL of whole blood was mixed with 20 μL of 0.2 M calcium chloride according to the manufacturer's protocol for citrated samples. The tests were performed after pre-warming the TEG analyser and quality control checks were performed routinely on a daily basis. To assure repetitive outcomes all tests were performed by a single operator trained in analysing and interpreting TEG results. TAVI operators remained blinded to TEG results.

TAVI procedural technique

The vascular access site for prosthesis delivery and type of device used was chosen by the first operator and was based on anatomical features of each individual patient. A pre-close suture-mediated device (Prostar®) was used in most of the patients with transfemoral access. The majority of the procedures where performed under general anaesthesia unless in patients with severe obstructive pulmonary disease. As well

as the delivery system access site, two central venous lines were obtained — one for intravenous drug administration and the second for temporary pacing electrode placement. Also, there was an additional arterial puncture (6 F), either transfemoral or transradial, for placing a pig-tail catheter for automated contrast injection during the procedure.

Periprocedural antithrombotic regimens

Regarding periprocedural pharmacological treatment, patients taking no anticoagulation, where given loading doses of 300 mg of aspirin and clopidogrel within 24 h before TAVI, and then continued with 75 mg daily after the procedure. Oral antiplatelet drugs were continued throughout the hospitalisation, unless major bleeding occurred. Patients on chronic OAC treatment were switched to low-molecular weight heparin at least 48 h before the start of the procedure. After TAVI they were treated with double therapy (either aspirin + OAC in patients without recent stent implantation or clopidogrel + OAC in patients with recent PCI), and the time of introduction of these drugs depended on the bleeding and vascular outcomes.

Unfractioned heparin was given as a 5000-IU IV bolus immediately after obtaining access for the delivery system, and additional boluses were given if the ACT value was below 250 s. Protamine sulphate was administered immediately after successful implantation of the bioprosthesis, at the discretion of the operator as 1 mg per 100 IU of UFH.

Study definitions and endpoints

Bleeding complications were defined according to Valve Academic Research Consortium-2 (VARC-2) criteria [10]. The primary endpoint of this study was to evaluate whether any one of the main TEG parameters is an independent predictor for in-hospital bleeding complications after TAVI.

Statistical analysis

Continuous variables, expressed as means ± standard deviation, were compared using Student's t-test or Mann-Whitney U-test depending on the distribution pattern. Shapiro-Wilk test was used to confirm or reject normal distribution of each continuous variable. Categorical variables, expressed as counts and percentages, were compared using χ^2 test or Fisher's exact test, as appropriate. In order to assess discrimination ability of TEG parameters in terms of predicting major and life-threatening bleeding, receiver-operating characteristic (ROC) analysis with an area under the curve (AUC [c-statistic]) was performed. A parameter with the largest AUC (AUC ≥ 0.7) was identified and selected for further analysis including optimal cut-off value determination. Univariate logistic regression analysis of the parameters that were different between the groups was used to identify predictors of the primary endpoint. Baseline variables with a p value ≤ 0.10 in the univariate analysis were included into a multivariate model in order to detect independent predictors of bleeding. Results are presented as odds ratio (OR) with 95% confidence interval (CI). All probability values reported are two-sided and a value < 0.05 was considered to be significant. All data were processed using SPSS software, version 22 (IBM SPSS Statistics, New York, US).

RESULTS

Transcatheter aortic valve implantation procedures were mainly performed in general anaesthesia (82%) and through transfemoral route (82%). The pre-close device for puncture site management was used in 31 (58%) cases, and protamine sulphate was administered in 15 (28%) cases. Among 54 patients treated with TAVI, major and life-threatening bleeding (MLTB) was present in 13 (24.1%), of which two (3.7%) were life threatening bleeding and 11 (20.4%) major according to VARC-2 criteria. Life-threatening bleeding consisted of one case of cardiac tamponade and one forearm haematoma with compartment syndrome. All major bleedings were at the femoral access site (four after surgical cut-down and seven after pre-close device). Those patients who developed MLTB had significantly higher prevalence of hypertension and chronic obstructive pulmonary disease (COPD), had lower left ventricular ejection fraction (LVEF) and received more units of UFH per kilogram (UFH IU/kg) (Table 1). There were no statistically significant differences between the MLTB and non-MLTB groups in terms of access site or technique chosen for arterial closure.

In ROC curve analysis, none of the TEG parameters analysed in the CK sample before the procedure or those assessed in CHK assays after TAVI were found to be significantly associated with bleeding complications (Figs. 2, 4). The only TEG parameters that showed significant sensitivity and specificity for predicting bleeding where those obtained in the CK sample at the end of the procedure. The following parameters were significant: R (AUC 0.690, 95% CI 0.50–0.88, p = 0.04), angle (AUC 0.751, 95% CI 0.59–0.92, p = 0.007), and maximum amplitude (MA) (AUC 0.771, 95% CI 0.62–0.93, p = 0.003; Fig. 3). MA showed highest AUC and was included in the further logistic regression model as both continuous and dichotomised variables based on the ROC curve cut-off (MA ≤ 46.6 mm). Parameters that were significantly different between groups above and below the MA cut-off value were identified and along with baseline significant variables became covariates in logistic regression analysis (Table 2). Initially, univariate logistic regression analysis was performed. Unfractioned heparin per kilogram (UFH IU/kg), COPD, LVEF, and MA were statistically significant for predicting bleeding. When confounding factors were included in the multivariate logistic regression analysis, MA independently predicted bleeding after TAVI, both as a continuous variable (p = 0.004; 95% CI 0.92–0.98; OR 0.95 per 1 mm increment) and dichotomised variable (p = 0.004; OR 10.4; 95% CI 2.1–51.8). The only other parameter, which also independently predicted bleeding, was UFH IU/kg (p = 0.028; OR 1.04; 95% CI 1.005–1.08; Table 2).

Table 1. Baseline and procedural characteristics according to the occurrence of major or life-threatening bleeding (MLTB)

	Total cohort (n = 54)	Bleeding (MLTB, n = 13)	No bleeding (non-MLTB, n = 41)	p
Medical history				
Age [years]	80.6 ± 6.6	77.8 ± 8.2	s81.5 ± 5.9	0.11
Female	30 (56%)	9 (69%)	21 (51%)	0.34
Body mass index [kg/m^2]	28.1 ± 5.1	27.1 ± 4	28.4 ± 5.4	0.55
Logistic EuroSCORE	21.8 ± 14.1	21.4 ± 13.9	22 ± 15	0.90
EuroSCORE II	6.5 ± 4.2	6.4 ± 4.2	6.6 ± 4.5	0.91
STS Score	8.5 ± 5.5	8.4 ± 5.5	8.6 ± 5.9	0.90
Hypertension	39 (72%)	13 (100%)	26 (63.4%)	0.01
Diabetes	18 (33%)	5 (39%)	13 (31.7%)	0.74
COPD	10 (19%)	5 (39%)	5 (12.2%)	0.048
Myocardial infarction	12 (22%)	5 (39%)	7 (17.1%)	0.13
PCI	17 (32%)	4 (31%)	13 (31.7%)	1
CABG	8 (15%)	2 (15%)	6 (14.6%)	1
Stroke/TIA	8 (15%)	1 (8%)	7 (17.1%)	0.66
Atrial fibrillation	23 (43%)	6 (46%)	17 (41.5%)	1
Chronic kidney disease	29 (54%)	7 (54%)	22 (53.7%)	0.99
Antithrombotics pre-TAVI				
SAPT	10 (19%)	3 (23%)	7 (17.1%)	0.69
DAPT	22 (41%)	3 (23%)	19 (46.3%)	0.20
LMWH/OAC	20 (37%)	5 (39%)	15 (36.6%)	1
Laboratory variables pre-TAVI				
Haemoglobin [g/dL]	12.2 ± 1.4	11.9 ± 1.1	12.3 ± 1.5	0.61
WBC [10^3/mm^3]	6.9 ± 2.3	6.5 ± 1.7	7.1 ± 2.5	0.52
Platelet count [10^3/mm^3]	189 ± 50	189 ± 51	188 ± 50	0.73
Creatinine [mg/dL]	1.4 ± 0.80	1.6 ± 0.94	1.4 ± 0.75	0.55
INR	1.15 ± 0.25	1.16 ± 0.27	1.14 ± 0.24	0.96
APTT [s]	33.3 ± 6.5	33 ± 5.8	33 ± 6.8	0.94
Fibrinogen [mg/dL]	352 ± 71	340 ± 64	355 ± 73	0.42
Echocardiography pre-TAVI				
PG mean [mmHg]	45 ± 12	42 ± 14	46 ± 12	0.28
PG max [mmHg]	79 ± 21	73 ± 22	80 ± 20	0.32
Ejection fraction [%]	55 ± 12	49 ± 13	58 ± 11	0.018
Vmax [s]	4.3 ± 0.85	4.3 ± 1.33	4.3 ± 0.64	0.95
AVA [cm^2]	0.73 ± 0.19	0.75 ± 0.28	0.72 ± 0.17	0.72
Procedural characteristics				
Protamine administered	15 (28%)	3 (31%)	11 (27%)	1
Transfemoral access	46 (85%)	11 (85%)	35 (85%)	0.95
Self-expandable valve	46 (85%)	12 (92%)	34 (83%)	0.41
Prostar	31 (57%)	7 (54%)	24 (59%)	0.77
Final ACT [s]	270 ± 54	288 ± 58	265 ± 52	0.24
UFH per patient [×10^3 IU]	7.6 ± 1.6	8.2 ± 2.3	7.4 ± 1.3	0.29
UFH per kg [IU/kg]	101 ± 24	117 ± 22	96 ± 23	0.005

ACT — activated clotting time; APTT — activated partial thromboplastin time; AVA — aortic valve area; CABG — coronary artery by-pass grafting; COPD — chronic obstructive pulmonary disease; DAPT — dual antiplatelet therapy; INR — international normalised ratio; LMWH — low molecular-weight heparin; OAC — oral anticoagulants; PCI — percutaneous coronary intervention; PG — pressure gradient; SAPT — single antiplatelet therapy; STS — Society of Thoracic Surgeons; TAVI — transcatheter aortic valve implantation; TIA — transient ischaemic attack; UFH — unfractionated heparin; WBC — white blood cells; Vmax — peak velocity

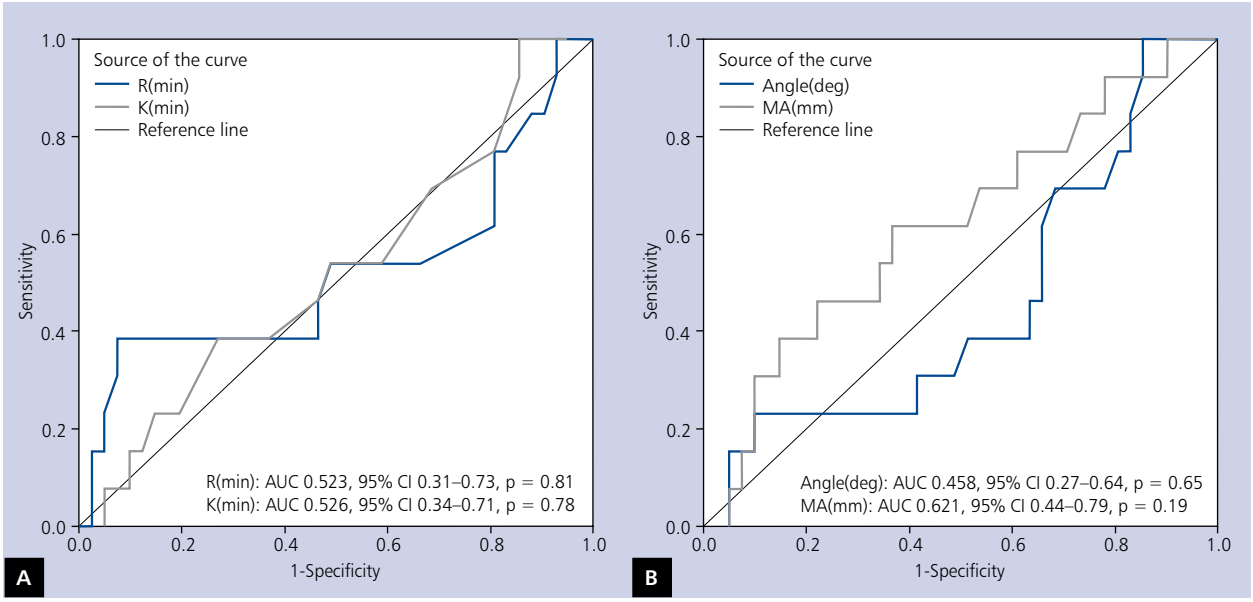

Figure 2. Receiver-operating characteristics curve (ROC) for predicting major and life-threatening bleeding in pre-procedural citrated kaolin thromboelastography (CK TEG); **A.** ROC curve for reaction time (R) and kinetics (K); **B.** ROC curve for angle and maximal amplitude (MA); angle — rate of clot formation; AUC — area under the curve; CI — confidence interval

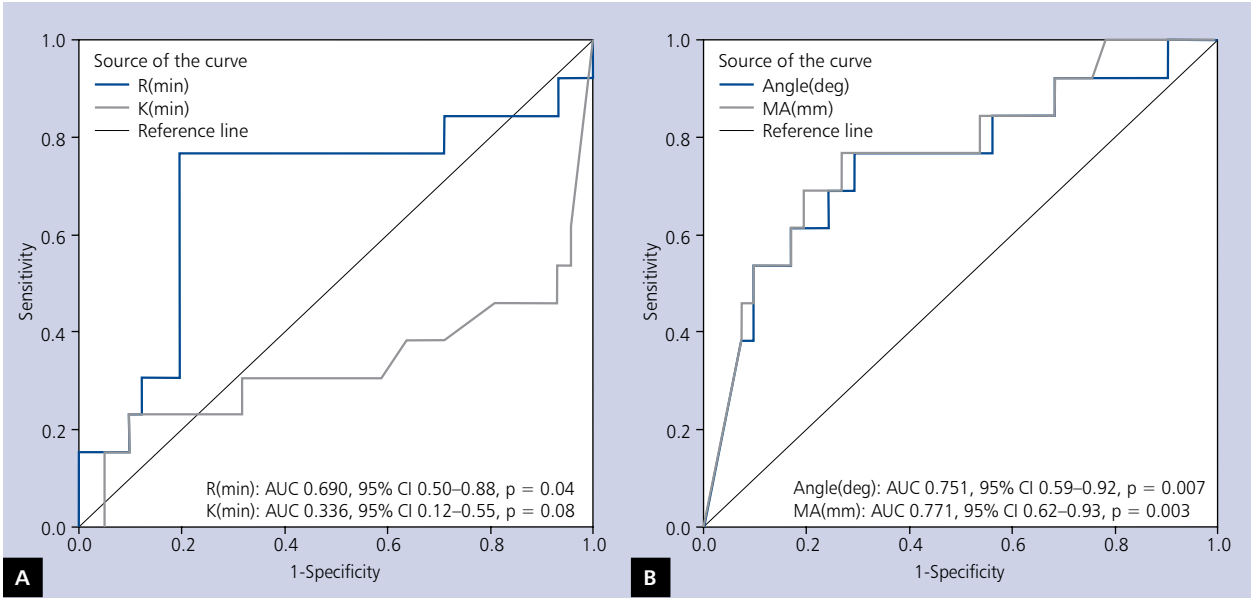

Figure 3. Receiver-operating characteristics curve (ROC) for predicting major and life-threatening bleeding in post-procedural citrated kaolin thromboelastography (CK TEG); **A.** ROC curve for reaction time (R) and kinetics (K); **B.** ROC curve for angle and maximal amplitude (MA); angle — rate of clot formation; AUC — area under the curve; CI — confidence interval

DISCUSSION

To the best of our knowledge this study is the first one to assess the use of thromboelastography in TAVI setting. It is a device that has proven clinical benefits in the field of traumatology and cardiac surgery by helping to reduce the amount of blood products used perioperatively and to predict bleeding incidence [11–15]. In our cohort of patients, we found that periprocedural viscoelastic testing may provide some prognostic value by predicting bleeding after TAVI. The most significant assay in our study was CK TEG after TAVI, showing the effect of

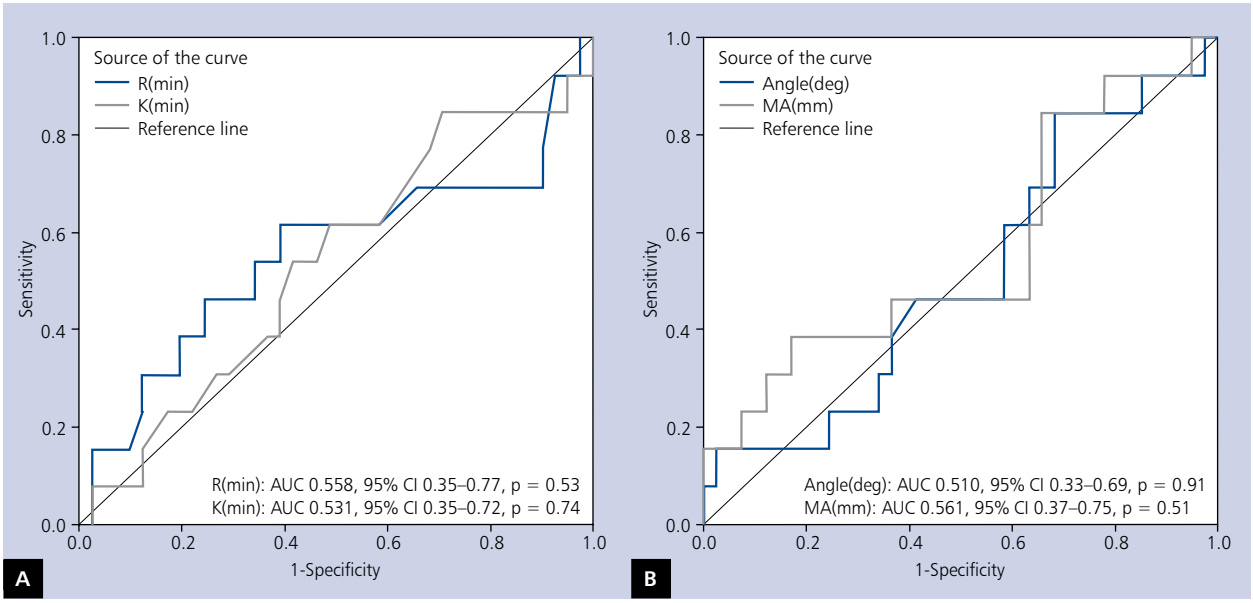

Figure 4. Receiver-operating characteristics curve (ROC) for predicting major and life-threatening bleeding in post-procedural citrated heparinised kaolin thromboelastography (CHK TEG); **A.** ROC curve for reaction time (R) and kinetics (K); **B.** ROC curve for angle and maximal amplitude (MA); angle — rate of clot formation; AUC — area under the curve; CI — confidence interval

Table 2. Logistic regression analysis of significant coefficients for major or life-threatening bleeding

	Univariate			Multivariate		
	P	OR	95% CI	P	OR	95% CI
COPD	0.04	4.5	1.05–19.3			
EF, per 1% increment	0.03	0.94	0.89–0.99			
MA per 1 mm increment	0.004	0.96	0.94–0.99	0.004	0.95	0.92–0.98
MA < 46.6 [mm]	0.003	9.1	2.1–39.3	0.004	10.4	2.1–51.8
UFH [IU/kg]	0.01	1.04	1.01–1.07	0.03	1.04	1.01–1.08

CI — confidence intervals; COPD — chronic obstructive pulmonary disease; MA — maximal amplitude; EF — ejection fraction; UFH — unfractionated heparin; OR — odds ratio; IU— international units

UFH on blood coagulation, with MA as a major independent predictor of bleeding. The same blood sample, when assessed in heparinised assay, showed no correlation with bleeding incidence. This finding is in parallel with the other independent predictor of bleeding (UFH IU/kg). Given that we found no difference between the MLTB and non-MLTB groups in terms of protamine given or ACT value at the end of procedure, CK TEG MA may provide more accurate insight into the activity of residual heparin after TAVI and relative heparin overdosing. This finding may prove especially important considering that most bleeding episodes in our cohort of patients occurred not during the procedure but instead due to slow oozing of the blood from the access site wound causing haematoma, pseudoaneurysm or overt bleeding. The lack of statistical significance between CK before and CHK sample after the procedure may suggest that even though some changes are present in blood composition [6] this remains without any relation to basic TEG tracings.

Despite recent advances in transcatheter valvular therapy, bleeding is a frequent complication after TAVI, and multiple investigations have been performed to elucidate the issue. In several studies, parameters that increased the risk of bleeding were chronic kidney disease, diabetes mellitus, or access site (typically transapical) [16–18]. None of the above-mentioned were found to be significant (or applicable) in our cohort of patients, but this may be explained by the small sample size. Another factor which has already been found to have significant impact on bleeding after TAVI is low body mass index (BMI < 20 kg/m^2) [19]. In the present study, we found no correlation between BMI and MLTB, but given that the MLTB group had received significantly higher doses of UFH per kilogram it may indicate one possible explanation of

the "obesity paradox" with respect to bleeding in the TAVI population. Given that the mean BMI in the study group was relatively high (28.1 ± 5.1 kg/m^2), this effect has to be confirmed in larger trials with equal representation of both high and low BMI groups.

The current valvular heart disease guidelines do not address the problem of periprocedural antithrombotic regimen nor the therapy that should be implemented later on. The postprocedural treatment currently used is based on schemes implemented in large randomised control trials [1–4], which consists of dual antiplatelet therapy for a period of one to six months. As for the periprocedural therapy, the types of drugs used (antiplatelet vs. antithrombotic), doses (loading doses vs. normal doses), or time of implementation (pre- vs. postprocedural) the evidence is still scarce and needs to be addressed in further studies.

Thromboelastography has been shown to predict both thromboembolic and bleeding events in different clinical scenarios [11–15]. Although being generally less specific and sensitive for assessing platelet function than aggregometry, it may still play a valuable role in diagnostics of coagulation abnormalities, especially in the setting of very heterogenous antithrombotic and antiplatelet therapy that is often found in TAVI cohorts. As in any other method requiring pipetting, sample preparation in TEG may result in difficulty to deliver reproducible results. In our study, in order to minimise this issue, a single well-trained technician was responsible for each test, and quality control tests were run on a daily basis. Currently, there are already new-generation thromboelastography devices available, with fully automated sample preparation, which should minimise the problem.

The most important limitation of this preliminary report is the relatively small sample size, but the study will be continued in a larger population

CONCLUSIONS

The strength of fibrin clot formation assessed in TEG immediately after bioprosthesis deployment has independent value for predicting bleeding in patients after TAVI. No other standard TEG parameters in different timeframes were able to foresee the haemorrhage. The results of this study, if confirmed in larger trials, may help to improve the perioperative care in patients after TAVI by recognising the patients that are at higher bleeding risk, and thus prompting more thorough evaluation.

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Conflicts of interest: *Zenon Huczek is proctor/speaker for Medtronic. Other authors have no conflicts of interest.*

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